Appendixes

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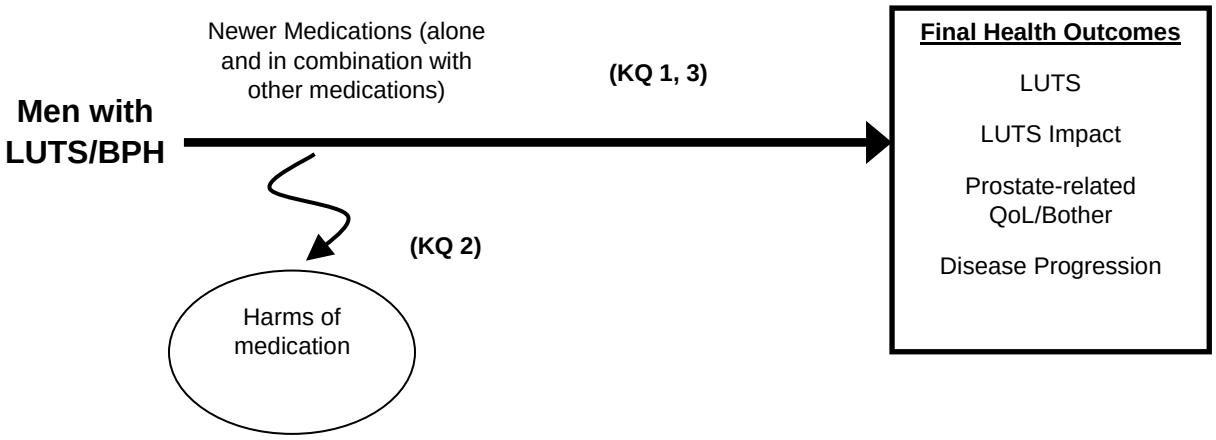
Appendix A. Analytical Framework and Search Strategies

Figure A1. Analytical Framework for Newer Medications for LUTS/BPH



Search Strategies

BPH Medline RCTs SRs Harms

1. *Prostatic Hyperplasia/
2. (hyperplasia adj3 prostat*).ti,ab.
3. hyperplasia of the prostate.ti,ab.
4. prostatic hyperplasia.ti,ab.
5. (hypertrophy adj3 prostat*).ti,ab.
6. (adenoma* adj3 prostat*).ti,ab.
7. exp *Lower Urinary Tract Symptoms/
8. lower urinary tract.ti,ab.
9. prostatism.ti,ab.
10. exp *Prostatism/
11. exp *Urinary Bladder Neck Obstruction/
12. bladder outlet obstruction.ti,ab.
13. (prostat* adj3 enlarg*).ti,ab.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. silodosin.mp.
16. 'KMD-3213'.ti,ab.
17. rapaflo.ti,ab.
18. 15 or 16 or 17
19. oxybutynin.ti,ab.
20. oxytrol.ti,ab.
21. 19 or 20
22. fesoterodine.ti,ab.
23. toviaz.ti,ab.
24. 22 or 23
25. darifenacin.ti,ab.
26. enablex.ti,ab.
27. 25 or 26
28. tolterodine.ti,ab.
29. detrol.ti,ab.
30. 28 or 29
31. solifenacin.ti,ab.
32. vesicare.ti,ab.
33. 31 or 32
34. trospium.ti,ab.
35. sanctura.ti,ab.
36. 34 or 35
37. mirabegron.ti,ab.
38. myrbetriq.ti,ab.
39. 37 or 38
40. tadalafil.ti,ab.
41. cialis.ti,ab.
42. 40 or 41
43. sildenafil.ti,ab.

44. viagra.ti,ab.
45. 43 or 44
46. avanafil.ti,ab.
47. stendra.ti,ab.
48. 46 or 47
49. vardenafil.ti,ab.
50. staxyn.ti,ab.
51. levitra.ti,ab.
52. 49 or 50 or 51
53. 18 or 21 or 24 or 27 or 30 or 33 or 36 or 39 or 42 or 45 or 48 or 52
54. 14 and 53
55. meta analysis as topic/
56. meta-analy$.tw.
57. metaanaly$.tw.
58. meta-analysis/
59. (systematic adj (review$1 or overview$1)).tw.
60. exp Review Literature as Topic/
61. or/55-60
62. cochrane.ab.
63. embase.ab.
64. (psychlit or psyclit).ab.
65. (psychinfor or psycinfo).ab.
66. or/62-65
67. reference list$.ab.
68. bibliograph$.ab.
69. hand search.ab.
70. relevant journals.ab.
71. manual search$.ab.
72. or/67-71
73. selection criteria.ab.
74. data extraction.ab.
75. 73 or 74
76. review/
77. 75 and 76
78. comment/
79. letter/
80. editorial/
81. animal/
82. human/
83. 81 not (82 and 81)
84. or/78-80,83
85. 61 or 66 or 72 or 77
86. 85 not 84
87. randomized controlled trials as topic/
88. randomized controlled trial/
89. random allocation/

90. double blind method/
91. single blind method/
92. clinical trial/
93. clinical trial, phase i.pt.
94. clinical trial, phase ii.pt.
95. clinical trial, phase iii.pt.
96. clinical trial, phase iv.pt.
97. controlled clinical trial.pt.
98. randomized controlled trial.pt.
99. multicenter study.pt.
100. clinical trial.pt.
101. exp Clinical trials as topic/
102. or/87-101
103. (clinical adj trial$).tw.
104. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
105. placebos/
106. placebo$.tw.
107. randomly allocated.tw.
108. (allocated adj2 random$).tw.
109. 103 or 104 or 105 or 106 or 107 or 108
110. 102 or 109
111. case report.tw.
112. case report.tw.
113. letter/
114. historical article/
115. 111 or 112 or 113 or 114
116. 110 not 115
117. 14 and 53
118. (ae or to or po or co).fs.
119. (safe or safety).ti,ab.
120. side effec*.ti,ab.
121. ((adverse or undesirable or harm* or serious or toxic or negative) adj3 (effect* or reaction* or event* or outcome*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
122. exp Product Surveillance, Postmarketing/
123. exp "Drug-Related Side Effects and Adverse Reactions"/
124. exp Adverse Drug Reaction Reporting Systems/
125. exp Clinical Trials, Phase IV as Topic/
126. exp Poisoning/
127. (toxicity or complication* or noxious or tolerability).ti,ab.
128. 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127
129. 117 and (86 or 116 or 128)
130. limit 129 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or editorial or

festschrift or historical article or in vitro or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or portraits or validation studies or video-audio media or webcasts)
131. 129 not 130
132. limit 131 to "all child (0 to 18 years)"
133. limit 132 to "all adult (19 plus years)"
134. 131 not 132
135. 134 or 133
136. 135 and ("166".mp. or 128) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
137. 135 and 86

BPH Embase RCTs SRs Harms
March 25, 2015
1. *Prostate hypertrophy/
2. (hyperplasia adj3 prostat*).ti,ab.
3. hyperplasia of the prostate.ti,ab.
4. prostatic hyperplasia.ti,ab.
5. (hypertrophy adj3 prostat*).ti,ab.
6. (adenoma* adj3 prostat*).ti,ab.
7. exp *Lower Urinary Tract Symptom/
8. lower urinary tract.ti,ab.
9. prostatism.ti,ab.
10. exp *Prostatism/
11. exp *Bladder Neck stenosis/
12. bladder outlet obstruction.ti,ab.
13. (prostat* adj3 enlarg*).ti,ab.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. silodosin.mp.
16. 'KMD-3213'.ti,ab.
17. rapaflo.ti,ab.
18. 15 or 16 or 17
19. oxybutynin.ti,ab.
20. oxytrol.ti,ab.
21. 19 or 20
22. fesoterodine.ti,ab.
23. toviaz.ti,ab.
24. 22 or 23
25. darifenacin.ti,ab.
26. enablex.ti,ab.
27. 25 or 26
28. tolterodine.ti,ab.
29. detrol.ti,ab.
30. 28 or 29
31. solifenacin.ti,ab.

32. vesicare.ti,ab.
33. 31 or 32
34. trospium.ti,ab.
35. sanctura.ti,ab.
36. 34 or 35
37. mirabegron.ti,ab.
38. myrbetriq.ti,ab.
39. 37 or 38
40. tadalafil.ti,ab.
41. cialis.ti,ab.
42. 40 or 41
43. sildenafil.ti,ab.
44. viagra.ti,ab.
45. 43 or 44
46. avanafil.ti,ab.
47. stendra.ti,ab.
48. 46 or 47
49. vardenafil.ti,ab.
50. staxyn.ti,ab.
51. levitra.ti,ab.
52. 49 or 50 or 51
53. 18 or 21 or 24 or 27 or 30 or 33 or 36 or 39 or 42 or 45 or 48 or 52
54. 14 and 53
55. meta analysis as topic/
56. meta-analy$.tw.
57. metaanaly$.tw.
58. meta-analysis/
59. (systematic adj (review$1 or overview$1)).tw.
60. or/55-59
61. cochrane.ab.
62. embase.ab.
63. (psychlit or psyclit).ab.
64. (psychinfor or psycinfo).ab.
65. or/61-64
66. reference list$.ab.
67. bibliograph$.ab.
68. hand search.ab.
69. relevant journals.ab.
70. manual search$.ab.
71. or/66-70
72. selection criteria.ab.
73. data extraction.ab.
74. 72 or 73
75. review/
76. 74 and 75
77. comment/

78. letter/
79. editorial/
80. animal/
81. human/
82. 80 not (81 and 80)
83. or/77-79,82
84. 60 or 65 or 71 or 76
85. 84 not 83
86. randomized controlled trials as topic/
87. randomized controlled trial/
88. random allocation/
89. double blind method/
90. single blind method/
91. clinical trial/
92. (clinical adj trial$).tw.
93. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
94. placebos/
95. placebo$.tw.
96. randomly allocated.tw.
97. (allocated adj2 random$).tw.
98. or/86-97
99. case report.tw.
100. case study.tw.
101. letter/
102. historical article/
103. 99 or 100 or 101 or 102
104. 98 not 103
105. (ae or to or po or co).fs.
106. (safe or safety).ti,ab.
107. side effec*.ti,ab.
108. ((adverse or undesirable or harm* or serious or toxic or negative) adj3 (effect* or reaction* or event* or outcome*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
109. exp Product Surveillance, Postmarketing/
110. exp "Drug-Related Side Effects and Adverse Reactions"/
111. exp Adverse Drug Reaction Reporting Systems/
112. exp Clinical Trials, Phase IV as Topic/
113. exp Poisoning/
114. (toxicity or complication* or noxious or tolerability).ti,ab.
115. 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114
116. 54 and (85 or 104 or 115)
117. limit 116 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
118. limit 117 to (adult <18 to 64 years> or aged <65+ years>)
119. 116 not 117
120. 119 or 118

121. limit 120 to (book or book series or conference abstract or conference proceeding or "conference review" or editorial or letter or note or short survey or trade journal)
122. 120 not 121
123. 122 and (104 or 115)
124. 122 and 85
125. 123 not 124
126. from 125 keep 1-461

Appendix B. Risk of Bias Instrument and Instructions

Selection Bias	
Did method of randomization create biased allocation to interventions (inadequate randomization)?	
Were all randomized participants analyzed in the group to which they were allocated?	
Were the groups similar at baseline regarding the most important prognostic indicators?	
Did method of allocation create a biased allocation to interventions (inadequate allocation concealment)?	
Risk of selection bias (inadequate randomization or allocation concealment):	**[Low, Unclear, High]**
Performance Bias	
Was the care provider blinded to the intervention?	
Were the participants blinded to the intervention?	
Risk of performance bias due to lack of participant and personnel blinding, intervention definition and fidelity?	**[Low, Unclear, High]**
Detection Bias	
Were the outcome assessors blinded to the intervention?	
Questionnaire Derived Outcomes: Was the scale used to measure outcomes validated, reliable?	
Were outcomes measured in clinically meaningful ways?	
Were co-interventions avoided or similar?	
Was the timing of the outcome assessment similar in all groups?	
Were estimates appropriately corrected for multiple comparisons?	
Risk of detection bias due to lack of outcome assessor blinding, outcomes measurement, statistical analysis, power?	**[Low, Unclear, High]**
Attrition Bias	
Was attrition lower than 20%?	
Reasons for incomplete/missing data adequately explained?	
Incomplete data handled appropriately?	
Risk of attrition bias due to amount, nature, or handling of incomplete outcome data?	**[Low, Unclear, High]**
Reporting Bias	
Was a select group of outcomes reported (compared to methods section, protocol)?	
What is the risk of reporting bias due to selective outcome reporting? [Low, Unclear, High]	
Other Sources of Bias	
Are there other risks of bias? If yes, describe them in the Notes.	
Overall risk of bias assessment by outcome(s)	**[Low, Moderate, High] and explanation (1-2 sentences)**

Appendix C. Excluded Studies

1. Abrams P, Kaplan S, De Koning Gans HJ, et al. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. Journal of Urology 2006 Mar; 175(3 Pt 1):999-1004; discussion *(No outcomes of interest).*
2. Athanasopoulos A, Gyftopoulos K, Giannitsas K, et al. Combination treatment with an alpha-blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. Journal of Urology 2003 Jun; 169(6):2253-6 *(Not RCT).*
3. Auerbach SM, Gittelman M, Mazzu A, et al. Simultaneous administration of vardenafil and tamsulosin does not induce clinically significant hypotension in patients with benign prostatic hyperplasia. Urology 2004 November; 64(5):998-1003 *(Duration<4 weeks).*
4. Bae JH, Kim SO, Yoo ES, et al. Efficacy and safety of low-dose propiverine in patients with lower urinary tract symptoms/benign prostatic hyperplasia with storage symptoms: A prospective, randomized, single-blinded and multicenter clinical trial. Korean Journal of Urology 2011 April; 52(4):274-8 *(No intervention of interest).*
5. Bechara A, Romano S, Casabe A, et al. Comparative efficacy assessment of tamsulosin vs. tamsulosin plus tadalafil in the treatment of LUTS/BPH. Pilot study. Journal of Sexual Medicine 2008 Sep; 5(9):2170-8 *(Not RCT).*
6. Chen JH, Yu QW, Shen J, et al. Effectiveness of combined therapy with terazosin and tolterodine for patients with benign prostatic hyperplasia. Journal of Shanghai Jiaotong University (Medical Science) 2011; 31(6):809-12 *(Not available in English).*
7. Choi H, Kim JH, Shim JS, et al. Comparison of the efficacy and safety of 5-mg once-daily versus 5-mg alternate-day tadalafil in men with erectile dysfunction and lower urinary tract symptoms. International Journal of Impotence Research 2015 Jan-Feb; 27(1):33-7 *(Not RCT).*
8. De Rose AF, Giglio M, Traverso P, et al. Combined oral therapy with sildenafil and doxazosin for the treament of non-organic erectile dysfunction refractory to sildenafil monotherapy. International Journal of Impotence Research 2002 Feb; 14(1):50-3 *(Not BPH).*
9. Donatucci CF, Brock GB, Goldfischer ER, et al. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open-label extension study. BJU International 2011 Apr; 107(7):1110-6 *(Not RCT).*
10. Gacci M, Corona G, Vignozzi L, et al. Metabolic Syndrome and Benign Prostatic Enlargement: A Systematic Review and Meta-Analysis. BJU international 2014; *(Not RCT).*
11. Giuliano F, Oelke M, Jungwirth A, et al. Tadalafil once daily improves ejaculatory function, erectile function, and sexual satisfaction in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia and erectile dysfunction: results from a randomized, placebo- and tamsulosin-controlled, 12-week double-blind study. Journal of Sexual Medicine 2013 Mar; 10(3):857-65 *(No outcomes of interest).*
12. Glina S, Roehrborn CG, Esen A, et al. Sexual function in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia: results of a 6-month, randomized, double-blind, placebo-controlled study of tadalafil coadministered with finasteride. Journal of Sexual Medicine 2015 Jan; 12(1):129-38 *(No outcomes of interest).*
13. Guven EO, Balbay MD, Mete K, et al. Uroflowmetric assessment of acute effects of sildenafil on the voiding of men with erectile dysfunction and symptomatic benign prostatic hyperplasia. International Urology & Nephrology 2009; 41(2):287-92 *(Duration<4 weeks).*
14. Johnson ITM, Markland AD, Goode PS, et al. Efficacy of adding behavioural treatment or antimuscarinic drug therapy to alpha-blocker therapy in men with nocturia. BJU International 2013 July; 112(1):100-8 *(No intervention of interest).*
15. Kraus SR, Dmochowski R, Albo ME, et al. Urodynamic standardization in a large-scale, multicenter clinical trial examining the effects of daily tadalafil in men with lower urinary tract symptoms with or without benign prostatic obstruction. Neurourology and Urodynamics 2010 June; 29(5):741-7 *(No outcomes of interest).*

16. MacDiarmid SA, Anderson RU, Armstrong RB, et al. Efficacy and safety of extended release oxybutynin for the treatment of urge incontinence: an analysis of data from 3 flexible dosing studies. Journal of Urology 2005; 174(4 Pt 1):1301-5; discussion 5 *(Not BPH).*

17. Marks LS, Gittelman MC, Hill LA, et al. Silodosin in the treatment of the signs and symptoms of benign prostatic hyperplasia: a 9-month, open-label extension study. Urology 2009 Dec; 74(6):1318-22 *(Not RCT).*

18. Mathias SD, Crosby RD, Nazir J, et al. Validation of the Patient Perception of Intensity of Urgency Scale in patients with lower urinary tract symptoms associated with benign prostatic hyperplasia. Value in Health 2014 Dec; 17(8):823-9 *(Not RCT).*

19. Ng CF, Wong A, Cheng CW, et al. Effect of vardenafil on blood pressure profile of patients with erectile dysfunction concomitantly treated with doxazosin gastrointestinal therapeutic system for benign prostatic hyperplasia. Journal of Urology 2008 Sep; 180(3):1042-6 *(Duration<4 weeks).*

20. Nieminen T, Tammela TL, Koobi T, et al. The effects of tamsulosin and sildenafil in separate and combined regimens on detailed hemodynamics in patients with benign prostatic enlargement. Journal of Urology 2006 Dec; 176(6 Pt 1):2551-6 *(Duration<4 weeks).*

21. Nishizawa O, Yamaguchi O, Takeda M, et al. Randomized controlled trial to treat benign prostatic hyperplasia with overactive bladder using an alpha-blocker combined with anticholinergics. LUTS: Lower Urinary Tract Symptoms 2011 April; 3(1):29-35 *(No intervention of interest).*

22. Porst H, McVary KT, Montorsi F, et al. Effects of once-daily tadalafil on erectile function in men with erectile dysfunction and signs and symptoms of benign prostatic hyperplasia.[Erratum appears in Eur Urol. 2011 Jun;59(6):1082]. European Urology 2009 Oct; 56(4):727-35 *(No outcomes of interest).*

23. Roehrborn CG, Kaminetsky JC, Auerbach SM, et al. Changes in peak urinary flow and voiding efficiency in men with signs and symptoms of benign prostatic hyperplasia during once daily tadalafil treatment. BJU International 2010 Feb; 105(4):502-7 *(No outcomes of interest).*

24. Rovner ES, Kreder K, Sussman DO, et al. Effect of tolterodine extended release with or without tamsulosin on measures of urgency and patient reported outcomes in men with lower urinary tract symptoms. Journal of Urology 2008 Sep; 180(3):1034-41 *(No outcomes of interest).*

25. Te AE. Should vardenafil be used for the treatment of lower urinary tract symptoms associated with BPH? Nature Clinical Practice Urology 2008; 5(10):536-7 *(Not RCT).*

26. Unknown. Oral desmopressin effective for nocturnal polyuria in men with benign prostatic hyperplasia. Journal of the National Medical Association 2011 May; 103(5):461 *(No intervention of interest).*

27. Wang CJ, Lin YN, Huang SW, et al. Low dose oral desmopressin for nocturnal polyuria in patients with benign prostatic hyperplasia: a double-blind, placebo controlled, randomized study. Journal of Urology 2011 Jan; 185(1):219-23 *(No intervention of interest).*

28. Yalcinkaya FR, Davarci M, Akcin S, et al. Urodynamic evaluation of acute effects of sildenafil on voiding among males with erectile dysfunction and symptomatic benign prostate. Turkish Journal of Medical Sciences 2012 December; 42(6):951-6 *(Duration<4 weeks).*

29. Yang Y, Zhao XF, Li HZ, et al. Efficacy and safety of combined therapy with terazosin and tolteradine for patients with lower urinary tract symptoms associated with benign prostatic hyperplasia: a prospective study. Chinese Medical Journal 2007 Mar 5; 120(5):370-4 *(Not RCT).*

Appendix D. Supporting Tables and Figures: Silodosin

Table D1. Risk of bias assessments: silodosin trials

Study	Overall Risk of Bias Assessment	Rationale
Choo, 2014[1]	Moderate	Randomization and concealment methods not reported, groups similar at baseline except for IPSS storage, double-blinded, low attrition, PP and ITT analyses
Pande, 2014[2]	Low	
Yokoyama, 2012[3]	Moderate	Randomization and concealment methods not reported, groups similar at baseline, unblinded, completer analysis, attrition not reported by group
Chapple, 2011[4]	Low	
Watanabe, 2011[5]	High	Randomization and concealment methods not reported, open label crossover design with no washout, planned analysis not reported, high attrition, only completer baseline and results data reported
Yokoyama, 2011[6]	Moderate	Randomization and concealment methods not reported, groups similar at baseline except for PVR, unblinded, attrition moderate and similar between groups, unclear how missing data handled
Yu, 2011[7]	Moderate	Randomization and concealment methods not reported, groups similar at baseline except for prostate volume and acute urinary retention, double-blinded, attrition moderate and similar between groups, PP and ITT analyses
Miyakita, 2010[8]	High	Randomization and concealment methods not reported, drug dosages differed between groups, groups similar at baseline except for heart rate, unblinded, crossover design with no washout, planned analysis not reported, high attrition which differed by group, both baseline and outcome data reported for per protocol population only
Marks, 2009[9]	Low	
Kawabe, 2006[10]	Moderate	Randomization and concealment methods not reported, groups similar at baseline except for QoL, different group sizes, attrition not reported but only one patient excluded from analysis, outcome reporting unclear

Table D2. Characteristics of BPH treatment, comparison, and population: silodosin trials

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Choo, 2014[1] Korea N=424	T_1: Silodosin 8 mg qd T_2: Silodosin 4 mg bid	12 wk	I: Age ≥ 50 yr; LUTS/BPH; IPSS ≥ 8; QoL-I ≥ 3; prostate volume ≥ 20 mL; Qmax <15 E: PVR ≥200 mL; history of prostatectomy, intrapelvic radiation, prostate cancer, or PSA >10 ng/mL; neurogenic bladder; active UTI; renal impairment, severe hepatic or cardiovascular disease; history of orthostatic hypotension; use of ABs within 2 wk or 5-ARIs within 3 mo	Mean age: 64 Race: NR Baseline IPSS: 19.0
Pande, 2014[2] India N=61	T: Silodosin 8 mg qd C: Tamsulosin 0.4 mg qd	12 wk	I: Age > 50 yr; LUTS from BPH; IPSS >7; treatment naïve E: LUTS but not BPH; acute retention of urine within 6 mo; elevated PSA, serious comorbidity; use of anticholinergic, androgenic or estrogenic medications; use of other α-adrenergic antagonists or diuretics; history of prostatic or urethral surgery, or substance abuse	Mean age: 62 Race: NR Baseline IPSS: 18.4
Yokoyama, 2012[3] Japan N=46	T: Silodosin 4 mg bid C: Tamsulosin 0.2 mg qd	13 wk	I: Age ≥50 yr; IPSS ≥8; QoL-I ≥3 E: History of prostate cancer, neurogenic bladder, or urethral stricture; active UTI or other complications likely to affect micturition; PSA >4 ng/mL; negative prostatic biopsy	Mean age: 70 Race: NR Baseline IPSS: 20.2
Chapple, 2011[4] Eisenhardt, 2014[11] Novara, 2014[12] Europe N=1336	T: Silodosin 8mg qd C_1: Placebo C_2: Tamsulosin 0.4 mg qd	12 wk	I: Age ≥50 yr; LUTS (IPSS ≥13); BOO (Qmax 4-15 mL/s and voided volume ≥125 mL); compliance 80%-120% during placebo run-in E: Improvement in the IPSS ≥25% during run-in; PVR ≥250 mL; intravesical obstruction from any cause other than BPH; history of any procedure for BPH, active UTI or recurrent UTIs; current prostatitis or chronic prostatitis; history of prostate or invasive bladder cancer, significant postural hypotension; use of 5-ARIs within 6 mo of an AB or phytotherapy within 2 wk	Mean age: 66 Race: 100% white Baseline IPSS: 19.1
Watanabe, 2011[5] Japan N=102	T: Silodosin 4 mg bid C: Tamsulosin 0.2 mg qd	4 wk	I: IPSS ≥8; QoL-I ≥2; LUTS/BPH; previously untreated E: NR	Mean age: 70 Race: NR Baseline IPSS: 17.3
Yokoyama, 2011[6] Japan N=90	T: Silodosin 4 mg bid C: Tamsulosin 0.2 mg qd	12 wk	I: Age 50-80 yr; IPSS ≥8 E: PSA >10, unless biopsy-negative for malignancy	Mean age: 71 Race: NR Baseline IPSS: 18.4

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Yu, 2011[7] Taiwan N=209	T: Silodosin 4 mg bid C: Tamsulosin 0.2 mg qd; placebo	12 wk	I: Age ≥40 yr; IPSS ≥13; HRQL ≥3; prostate volume ≥20 mL; Qmax <15 mL/s; voided volume ≥100 mL E: Previous prostate surgery, prostate cancer, neurogenic bladder, bladder neck constriction, urethral stricture, bladder calculus; active UTI; PVR >250 mL; exposure to sex hormone within 3 mo; serum creatinine >2.0 mg/dL; severe liver or cardiovascular disease, severe hypotension; hypersensitivity; substance or alcohol abuse within 2 yr	Mean age: 67 Race: NR Baseline IPSS: 19.6
Miyakita, 2010[8] Japan N=97	T: Silodosin 4 mg bid C: Tamsulosin 0.2 mg qd	4 wk	I: IPSS ≥8; QoL-I ≥3; prostate volume ≥20 mL; void volume ≥100 mL; Qmax <15 mL/s E: lpha1-blocker use for hypertension, or for BPH within 2 mo; vardenafil use; inappropriate as judged by attending physician	Mean age: 69 Race: NR Baseline IPSS: 17.4
Marks, 2009[9] Marks, 2013[13] Gittelman, 2011[14] Kapla,n 2011[15] Roehrborn, 2011[16] Eisenhardt, 2014[11] Novara, 2014[12] USA N=923	T: Silodosin 8 mg qd C: Placebo	12 wk	I: Age ≥50 yr; IPSS ≥13; Qmax 4 -15 mL/s; PVR <250 mL E: Use of alpha-adrenoceptor antagonists or 5-ARIs; intravesical obstruction unrelated to BPH; bladder calculi; history of or current condition affecting bladder function; prior surgical intervention to relieve BPH or bladder neck obstruction; active UTI or history of recurrent UTI within 2 yr; prostatitis within 3 mo; BPH unrelated urinary retention within 3 mo; recurring prostatitis; prior or current prostate cancer or PSA >10 ng/mL; prior invasive bladder cancer; bladder catheterization or bladder or prostate instrumentation within 30 d and history of or current significant postural hypotension, including changes in systolic or diastolic blood pressure or heart rate, and lightheadedness, fainting, blurred vision, profound weakness, or syncope upon change in position	Mean age: 65 Race: 89% white Baseline IPSS: 21.3
Kawabe, 2006[10] Homma, 2010[17] Japan N=631	T: Silodosin 4 mg bid C_1: Placebo C_2: Tamsulosin 0.2 mg qd	12 wk	I: Age ≥50 yr; IPSS of ≥8; QoL-I ≥3; LUTS/ BPH (by digital rectal examination or ultrasound); prostate volume ≥20 mL; Qmax <15 mL/s; voided volume ≥100 mL; PVR <100 mL; outpatients E: Use of antiandrogens within 1 yr; prostatectomy, intrapelvic radiation, or prostatic hyperthermia; prostate cancer or suspected prostate cancer; neurogenic bladder, bladder neck constriction, urethral stricture, bladder calculus, severe bladder diverticulum, active UTI, serum creatinine ≥2.0 mg/dL, other complications affecting micturition; severe hepatic or cardiovascular disease; orthostatic hypotension	Mean age: 65 Race: NR Baseline IPSS: 17.1

AB=alpha blocker; ARI=alpha-reductase inhibitor; bid=twice daily; BOO=bladder outlet obstruction; BPH=benign prostatic hyperplasia; d=days; C=comparator group; C_1=comparator group 1; C_2=comparator group 2; dL=deciliters; E=exclusion criteria; HRQL=health-related quality of life; I=inclusion criteria; IPSS=International Prostate Symptom Score; LUTS=lower urinary tract symptoms; mg=milligrams; mL=milliliters; ng=nanograms; NR=not reported; PSA=prostate-specific antigen; PVR=postvoid residual urine; qd=daily; Qmax=maximum urinary flow rate; QoL=quality of life; QoL-I=International Prostate Symptom Score-QoL Item; s=seconds; T=treatment group; T_1=treatment group 1; T_2=treatment group 2; UTI=urinary tract infection; wk=weeks; yr=years

Table D3. Strength of evidence assessments: silodosin efficacy and adjunctive efficacy

Comparison	Outcome	# Trials (n)	Summary statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Silodosin, 8 mg vs. placebo	IPSS/AUA-SI , *mean change from baseline*	4 (1743)	WMD = -2.68 (-3.24 to -2.11)	Low	Direct	Imprecise	Consistent	Undetected[a]	Moderate
	Responders ≥ 25% reduction in IPSS scores	2 (819)	RR = 1.38 (1.21 to 1.57)	Low	Direct	Precise	Consistent	Undetected[a]	High
	IPSS QoL, reporting "delighted, pleased, or mostly satisfied'	2 (1494)	RR = 1.36 (1.21 to 1.57)	Low	Direct	Precise	Consistent	Undetected[a]	High
	IPSS QoL, *mean change from baseline*	1 (264)	MD = -0.60 (-0.92 to -0.28) SMD = -0.45 (-0.71 to -0.19)	Low	Direct	Imprecise	Consistent (same direction as dictomous QoL outcomes)	Undetected[a]	Moderate
	Overall withdrawals	2 (1494)	RR 1.1 (0.52 to 1.96)	Low	Direct	Imprecise	Inconsistent	Undetected[a]	Low
	Withdrawals due to adverse effects	3 (1759)	Greater with silodosin RR = 2.41 (1.41 to 4.12)	Low	Direct	Precise	Consistent	Undetected[a]	High
	Participants with ≥1 adverse effect	3 (1757)	Greater with silodosin RR = 1.38 (1.19 to 1.60)	Low	Direct	Precise	Consistent	Undetected[a]	High

[a] We searched and screened results from clinicaltrials.gov. We identified five silodosin trials registered with clinicaltrials.gov; one registered trial could not be traced to a publication (NCT01222650); one included trial could not be traced to registration (Kwabe 2006); also identified a phase 2 trial in FDA documents that we did not identify a publication for. Results for IPSS appeared consistent with those of published trials. We detected no publication bias.

ARD=absolute risk difference; ARR=absolute risk reduction; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference
* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

Table D4. Strength of evidence assessments: silodosin comparative effectiveness

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Silodosin, 8 mg vs. tamsulosin 0.2 to 0.4 mg	IPSS/AUA-, *mean change from baseline*	7 (1538)	WMD -0.64 (-1.46 to 0.18)	Moderate	Direct	Precise	Consistent	Undetected[a]	Moderate
	Responders – 25% reduction in IPSS scores	3 (1283)	RR 1.07 (0.99 to 1.15)	Moderate	Direct	Precise	Consistent	Undetected[a]	Moderate
	IPSS QoL, reporting "delighted, pleased, or mostly satisfied'	1 (765)	RR 0.98 (0.83 to 1.15)	Low	Direct	Precise	Unknown	Undetected[a]	Low
	IPSS QoL, *mean change from baseline*	5 (728)	WMD -0.16 (-0.54 to 0.23) SMD -0.13 (-0.46 to 0.20)	Moderate	Direct	Precise	Inconsistent	Undetected[a]	Low
	Overall withdrawals	4 (1125)	RR 1.05 (0.72, 1.52)	Moderate	Direct	Precise	Consistent	Undetected[a]	Low
	Withdrawals due to adverse effects	3 (1222)	RR 1.96 (1.08 to 3.55)	Moderate	Direct	Precise	Consistent	Undetected[a]	Moderate
	Participants with ≥1 adverse effect	3 (1338)	RR 1.11 (1.01 to 1.22)	Moderate	Direct	Precise	Consistent	Undetected[a]	Low

[a] We searched and screened results from clinicaltrials.gov. We identified five silodosin trials registered with clinicaltrials.gov; one registered trial could not be traced to a publication (NCT01222650); one included trial could not be traced to registration (Kwabe 2006); also identified a phase 2 trial in FDA documents that we did not identify a publication for. Results for IPSS appeared consistent with those of published trials. We detected no publication bias.

ARD=absolute risk difference; ARR=absolute risk reduction; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

Analysis Figures for Silodosin

Figure D1. IPSS responders (≥25 decrease from baseline): silodosin vs. placebo

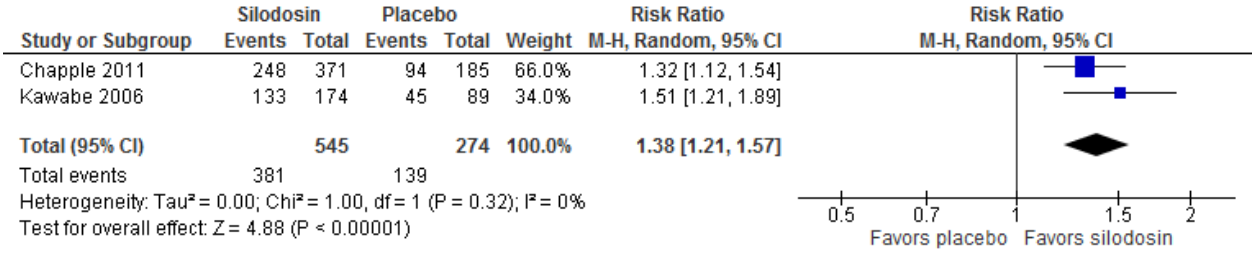


Figure D2. IPSS scores, mean change from baseline: silodosin vs. placebo

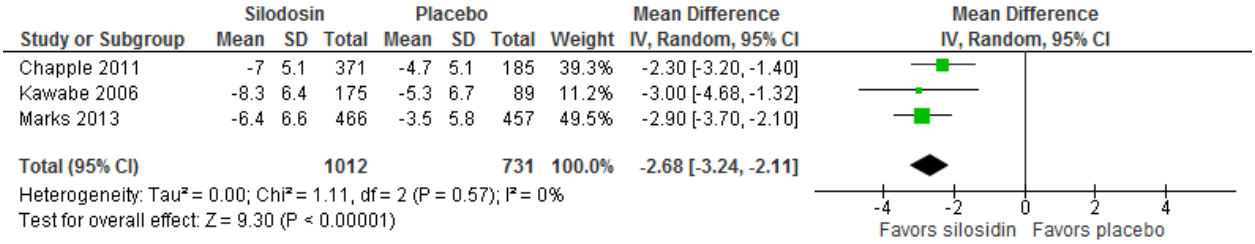


Figure D3. IPSS QoL, reporting 'delighted, pleased, or mostly satisfied': silodosin vs. placebo

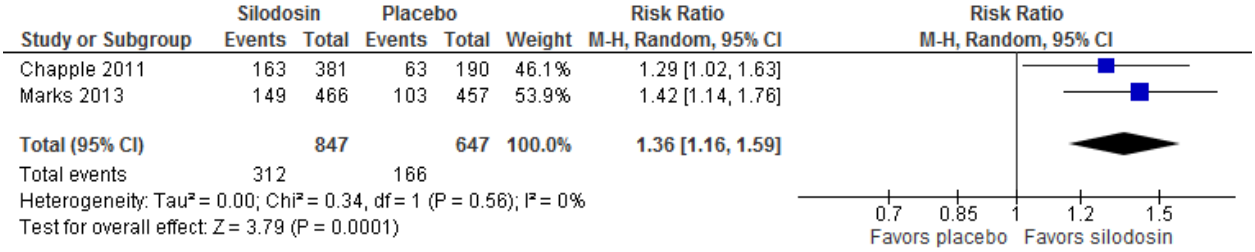


Figure D4. Overall withdrawals: silodosin vs. placebo

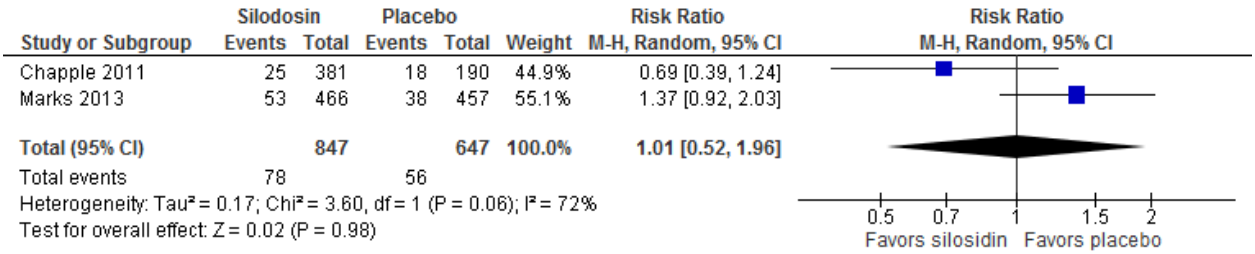


Figure D5. Withdrawals due to adverse effects: silodosin vs. placebo

Study or Subgroup	Silodosin Events	Silodosin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Chapple 2011	8	381	3	190	16.5%	1.33 [0.36, 4.96]
Kawabe 2006	18	176	4	89	25.8%	2.28 [0.79, 6.52]
Marks 2013	30	466	10	457	57.7%	2.94 [1.46, 5.95]
Total (95% CI)		**1023**		**736**	**100.0%**	**2.41 [1.41, 4.12]**
Total events	56		17			

Heterogeneity: Tau² = 0.00; Chi² = 1.10, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 3.23 (P = 0.001)

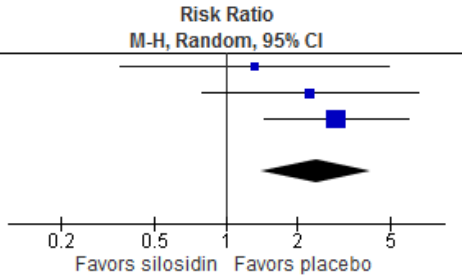


Figure D6. Participants with ≥1 adverse effect: silodosin vs. placebo

Study or Subgroup	Silodosin Events	Silodosin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Chapple 2011	133	381	46	190	19.0%	1.44 [1.08, 1.92]
Kawabe 2006	155	175	63	88	40.9%	1.24 [1.07, 1.43]
Marks 2013	257	466	168	457	40.1%	1.50 [1.30, 1.74]
Total (95% CI)		**1022**		**735**	**100.0%**	**1.38 [1.19, 1.60]**
Total events	545		277			

Heterogeneity: Tau² = 0.01; Chi² = 4.15, df = 2 (P = 0.13); I² = 52%
Test for overall effect: Z = 4.23 (P < 0.0001)

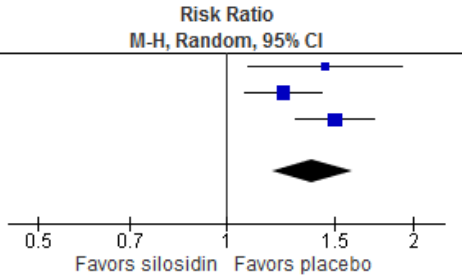


Figure D7. IPSS responders (≥25 decrease from baseline): silodosin vs. tamsulosin

Study or Subgroup	Silodosin Events	Silodosin Total	Tamsulosin Events	Tamsulosin Total	Weight	Risk Ratio M-H, Random, 95% CI
Chapple 2011	248	371	246	376	42.7%	1.02 [0.92, 1.13]
Kawabe 2006	133	174	126	192	28.6%	1.16 [1.02, 1.33]
Yu 2011	75	87	68	83	28.7%	1.05 [0.92, 1.20]
Total (95% CI)		**632**		**651**	**100.0%**	**1.07 [0.99, 1.15]**
Total events	456		440			

Heterogeneity: Tau² = 0.00; Chi² = 2.44, df = 2 (P = 0.30); I² = 18%
Test for overall effect: Z = 1.72 (P = 0.08)

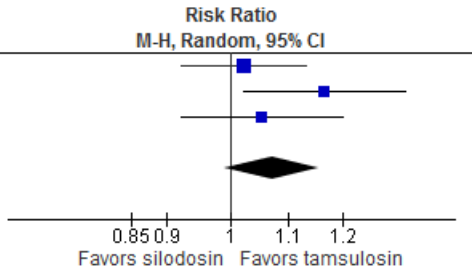


Figure D8. IPSS scores, mean change from baseline: silodosin vs. tamsulosin

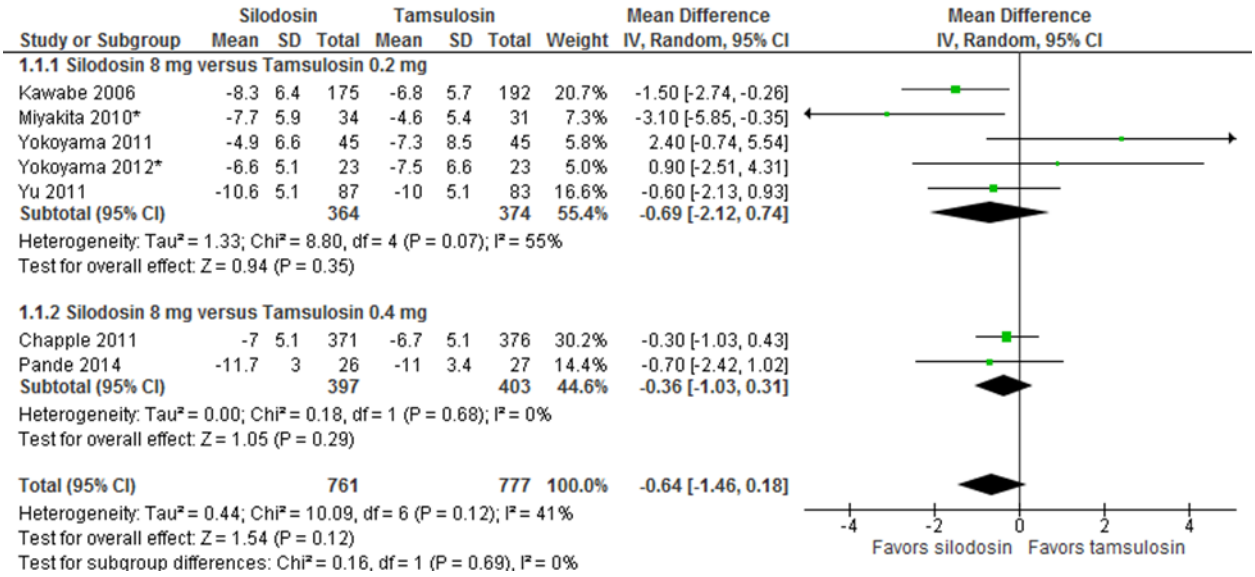


Figure D9. IPSS QoL scores, mean change from baseline: silodosin vs. tamsulosin

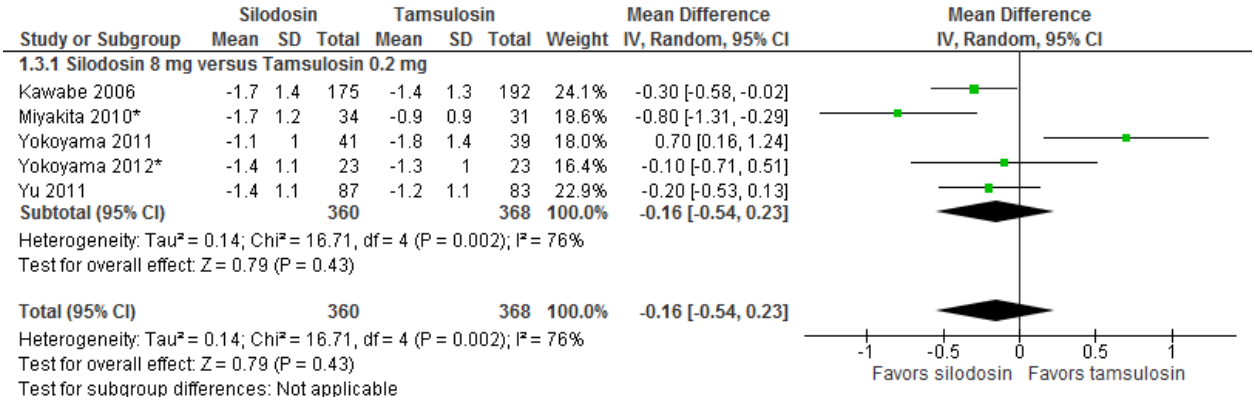


Figure D10. Overall withdrawals: silodosin vs. tamsulosin

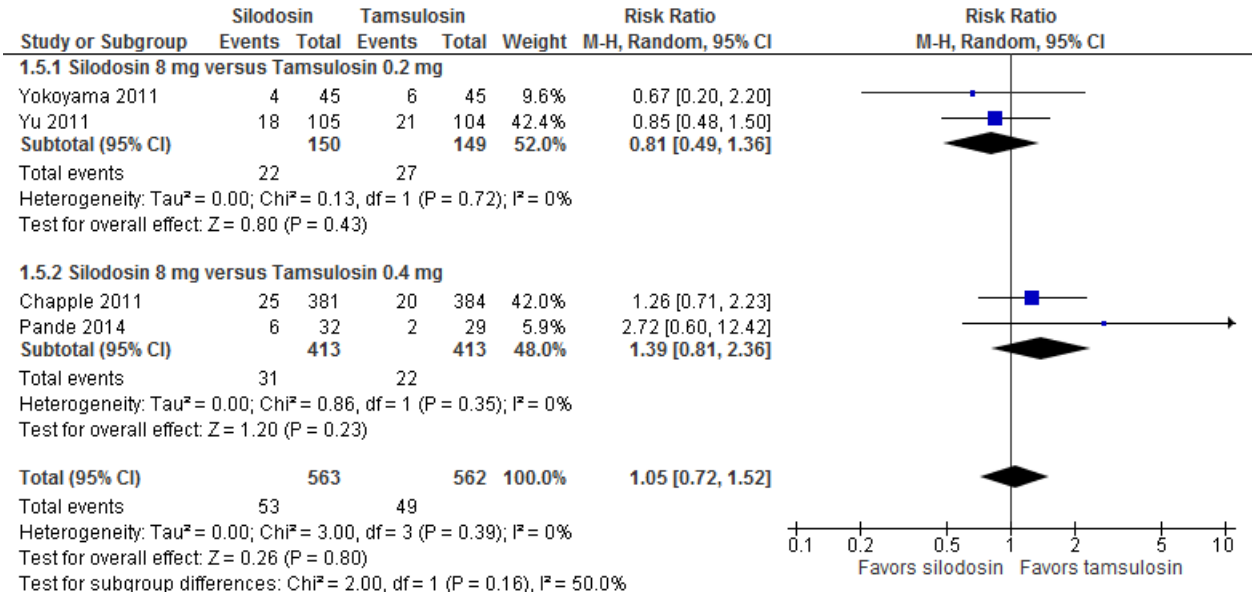


Figure D11. Withdrawals due to adverse effects: silodosin vs. tamsulosin

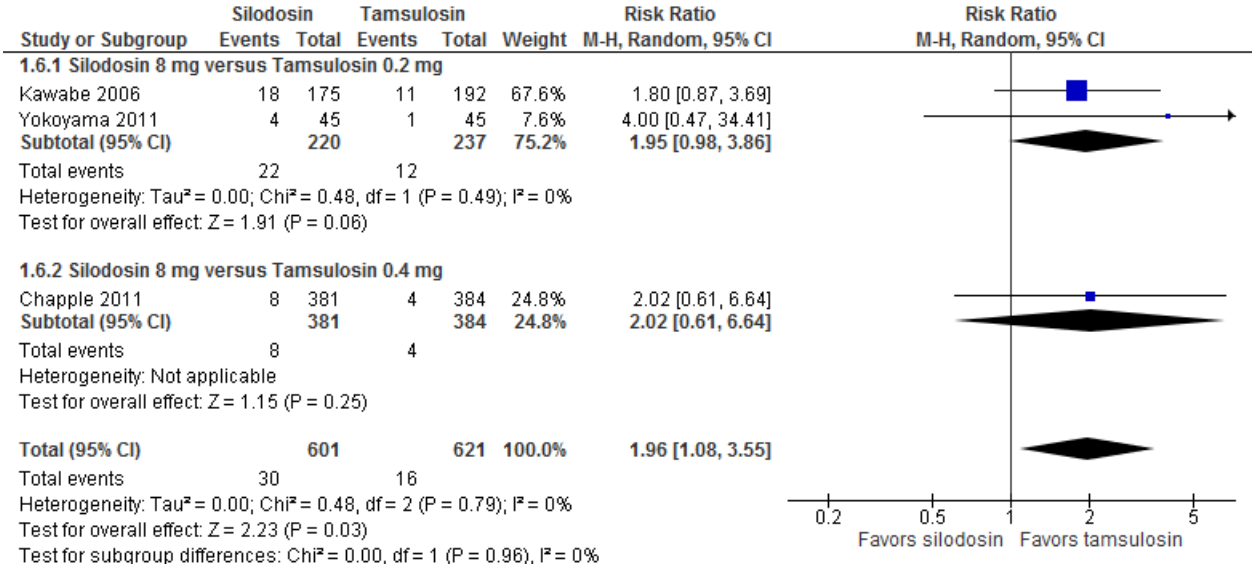
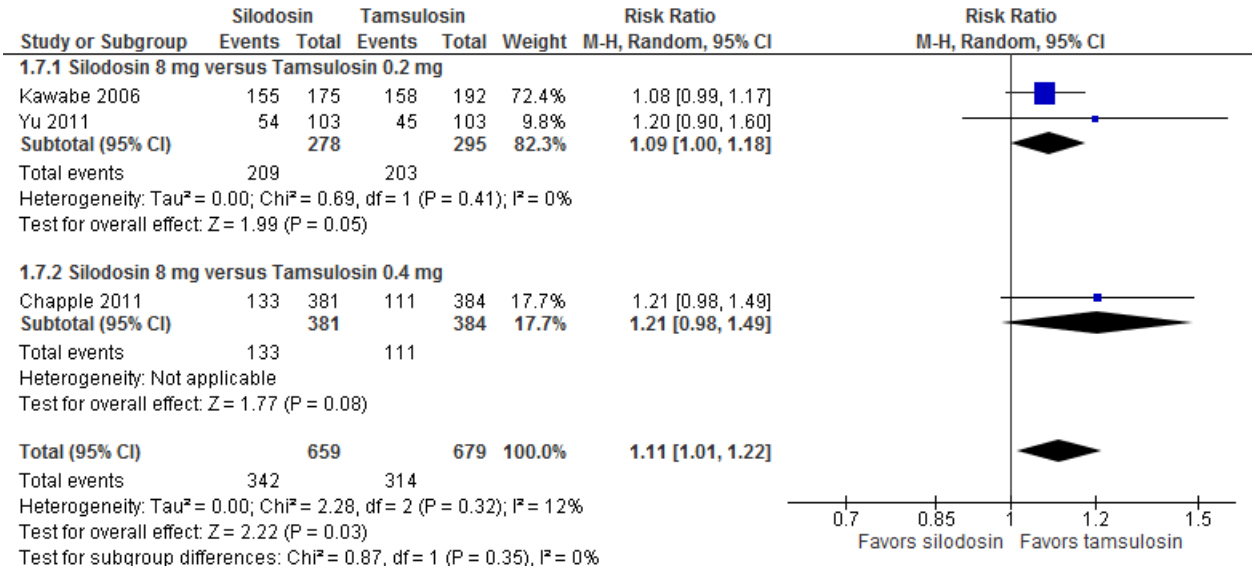


Figure D12. Participants with ≥1 adverse effect: silodosin vs. tamsulosin



Appendix E. Supporting Tables and Figures: Anticholinergics

Table E1. Risk of bias assessments: anticholinergic trials

Study	Overall Risk of Bias Assessment	Rationale
Liao, 2015[18]	High	Not blinded
Ko, 2014[19]	High	Randomization and allocation methods unclear, open label, outcome assessor blinding not described, moderate attrition, attrition higher in treatment group
Lee, 2014[20]	Low	
Memon, 2014[21]	High	Participants purposively selected, blinding methods not described, outcome assessor blinding not reported, attrition not reported
Kaplan, 2013[22]	Low	
Van Kerrebroeck, 2013a[23]	Moderate	Randomization and allocation concealment unclear.
Van Kerrebroeck, 2013b[24]	Low	
Ceylan, 2012[25]	Moderate	Randomization and allocation methods unclear, outcome assessor blinding not reported, attrition not reported
Konstantinidis, 2012[26]	High	Randomization and allocation not mentioned, blinding not mentioned, attrition unclear, small sample size
Malkoc, 2012[27]	Moderate	Randomization and allocation methods unclear, outcome assessor blinding not reported, moderate attrition, patients with severe side effects excluded, small sample size
Chung, 2011[28]	High	Allocation methods unclear, blinding methods not reported
Kaplan, 2011[29]	Moderate	Randomization and allocation concealment unclear.
Lee, 2011[30]	Low	
Seo, 2011[31]	Moderate	Randomization and allocation methods unclear, blinding methods unclear, adverse events not reported
Yamaguchi, 2011[32]	Low	
Chapple, 2009[33]	Low	
Kaplan, 2009[34]	Moderate	Randomization and allocation methods unclear, outcome assessor blinding not reported
MacDiamid, 2008[35]	Low	
Kaplan, 2006[36]	Low	

Table E2. Characteristics of BPH treatment, comparison, and population: anticholinergic trials

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Liao, 2015[18] Taiwan N=202	T: Tolterodine 4 mg C: Doxazosin 4 mg	12 wk	I: Age ≥40 yr; IPSS ≥8; predominant storage LUTS (IPSS-S ≥IPSS-V); PVR ≤250 mL E: PSA level >10 ng/mL; history of urinary retention, urodynamically proven detrusor underactivity, active UTI, urinary stone, documented genitourinary cancer, or previous transurethral surgery; antimuscarinics or 5a-reductase inhibitors within 6 mo	Mean age: 69 Race: NR Baseline IPSS: 11.5
Ko, 2014[19] Korea N=187	T: Solifenacin 5 mg; tamsulosin 0.2 mg C: Tamsulosin 0.2 mg	12 wk	I: Age >40 yr; LUTS (IPSS >12); urinary frequency (≥8/d), urgency (≥1/d), and symptoms on 3 d voiding diary E: Urologic malignancy; UTI; medical renal disease; medical liver disease; clinically significant BOO (residual urine >100 mL)	Mean age: 61 Race: NR Baseline IPSS: 19.3
Lee, 2014[20] Korea N=156	T: Solifenacin 5 mg; tamsulosin 0.2 mg C: Tamsulosin 0.2 mg qd	12 wk	I: Age ≥50 yr; total IPSS ≥14; IPPS-V ≥8; IPSS-S ≥6; QoL-I ≥3; micturition frequency ≥8 micturitions per 24 hr; urgency (≥1 micturition with urgency rating 3 per 24 hr); prostate volume ≥20; Qmax ≤15 mL/s; voided volume ≤125 mL E: Neurogenic bladder dysfunction; confirmed prostate cancer; acute or chronic urinary retention status; acute or chronic prostatitis within the previous 3 mo; PSA levels >10 ng/mL; history of recurrent UTI or bladder stones; previous BPH treatment; previous surgical intervention related to BOO	Mean age: 61 Race: NR Baseline IPSS: 17.9
Memon, 2014[21] Pakistan N=70	T: Tolterodine 2 mg bd; alfuzosin 10 mg hs C: Alfuzosin 10 mg hs	12 wk	I: Age >40 yr; BPH diagnosed on ultrasound scan having OAB symptoms; IPSS = 15-30 for >3 mo E: PVR >100 mL; Qmax <5 mL; conditions affecting bladder function like multiple sclerosis, spinal cord injury, or Parkinson's disease; history of Parkinson's disease, prostatic cancer, indwelling catheter, or use of anti-muscarinic or Abs	Mean age: NR Race: NR Baseline IPSS: 23.7
Kaplan, 2013[22] USA N=222	T: Solifenacin 6 mg; tamsulosin 0.4 mg T_2: Solifenacin 9 mg; tamsulosin 0.4 mg C: Placebo	12 wk	I: Age ≥45 yr; completed 3 d micturition diary; voiding and storage LUTS ≥3 mo; IPSS ≥8; BOOI ≥20; Qmax ≤12 mL/s, maximum voided volume ≥120 mL E: Indwelling urinary catheter; history of urinary retention >12 mo, carcinoma or pelvic radiation therapy, neurogenic bladder, chronic inflammation, stone in bladder/ureter, outflow tract obstruction, uncontrolled narrow-angle glaucoma, myasthenia gravis, urinary or gastric retention, bladder neck surgery, or diabetic neuropathy; contraindicated for use of anticholinergics; current UTI; recurrent UTI >3 episodes within 12 mo; previous/planned prostate surgery; hypersensitivity to solifenacin succinate or other anticholinergics, or tamsulosin hydrochloride	Mean age: 64 Race: 98% white Baseline IPSS: 17.8

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Van Kerrebroeck, 2013a[23] Netherlands N=937	T_1: Solifenacin 3 mg; tamsulosin 0.4 mg T_2: Solifenacin 6 mg; tamsulosin 0.4 mg T_3: Solifenacin 9 mg; tamsulosin 0.4 mg T_4: Solifenacin 3 mg T_5: Solifenacin 6 mg T_6: Solifenacin 9 mg C_1: Tamsulosin 0.4 mg C_2: Placebo	12 wk	I: IPSS ≥13; Qmax = 4–15 mL/s; volume voided during free flow ≥120 mL E: PVR >200 mL; UTI; history of specific urinary conditions (including urinary retention); previous bladder neck or prostate surgery	Mean age: 65 Race: 100% white Baseline IPSS: 18.5
Van Kerrebroeck, 2013b[24] Netherlands N=1334	T_1: Solifenacin 6 mg; tamsulosin 0.4 mg T_2: Solifenacin 9 mg; tamsulosin 0.4 mg C_1: Placebo C_2: Tamsulosin 0.4 mg	12 wk	I: Age ≥45 yr; storage and voiding symptoms; LUTS ≥3 mo; IPSS ≥ 13; Qmax = 4–12 mL/s; voided volume ≥120 mL during free flow; ≥2 urgency episodes per 24 hr (PPIUS grade 3 or 4); ≥ 8 micturitions per 24 hr before randomization E: Ultrasound-estimated prostate weight ≥75 g; UTI; history of specific urinary conditions; PVR >150 mL	Mean age: 65 Race: 99% white Baseline IPSS: 18.7
Ceylan, 2012[25] Turkey N=101	T: Darifenacin 7.5 mg; doxazosin 4 mg C: Doxazosin 4 mg	12 wk	I: Age >50 yr; IPSS >12; >8 micturitions per 24 hr; urgency >3 episodes per 24 hr; some moderate problems related to their bladder condition reported E: PVR >150 mL; Qmax <5 mL/s; previous prostatic surgery; PSA >10 ng/mL; bladder stone; diverticula; UTI; urethral stricture; neurogenic bladder; diabetes mellitus; previously treated with α-adrenergic antagonist, antimuscarinic agents, or diuretic medicine; histopathological prostate cancer diagnosis; PSA = 4-10 ng/mL; transrectal ultrasound guided prostatic biopsy	Mean age: 64 Race: NR Baseline IPSS: 16.3
Konstantinidis, 2012[26] Greece N=47	T: Fesoterodine 4 mg; tamsulosin 0.4 mg C: Tamsulosin 0.4 mg	6 wk	I: Age ≥50 yr; LUTS storage symptoms from suspected OAB and BOO E: PVR ≥200 mL; IPSS <12; Qmax ≤10 mL/s; prostate volume ≤60 cm^3; PSA ≥4 ng/mL; history of neurological diseases, other medications for LUTS (e.g. 5 α-reductase agents), bladder surgical interventions, AUR, glaucoma, and hepatic or renal failure	Mean age: 64 Race: NR Baseline IPSS: 16.0
Malkoc, 2012[27] Turkey N=58	T: Trospium chloride 45 mg; terazosin 5 mg C: Placebo; terazosin 5 mg	12 wk	I: Age >45 yr; OAB symptoms (urgency and mean urinary frequency ≥8 times per 24 hr with or without urinary incontinence) E: History of neurologic diseases, previous use of anticholinergic or alpha adrenergic blocker, PVR ≥100 mL, prostate volume >50 mL; history of AUR requiring catheterization; prostatic surgery; prostate cancer; PSA >4 ng/mL; UTI; diabetes	Mean age: 58 Race: NR Baseline IPSS: 15.3

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Chung, 2011[28] Taiwan N=137	T: Tolterodine ER 4 mg qd; doxazosin ER 4 mg qd and or dutasteride 0.5 mg qd C: Doxazosin ER 4 mg qd and or dutasteride 0.5 mg qd	52 wk	I: Age ≥70 yr; IPSS >8; IPSS-S >5; QoL-I >3; prostate volume >20 mL; Qmax <15 mL/s; urodynamic confirmed BPH/BOO E: Abnormal digital rectal examination; history of medical therapy or surgery for BPH; past or current use of ABs, finasteride or antimuscarinic agents; UTI; indwelling urethral catheter and previous urinary retention; PVR >250 mL; history of malignancy of genitourinary tract, neurological diseases (stroke, diabetes, multiple sclerosis, Parkinson's disease), symptomatic congestive heart failure, or chronic kidney disease	Mean age: 75 Race: NR Baseline IPSS: NR
Kaplan, 2011[29] USA N=943	T: Flexible-dose fesoterodine 4 or 8 mg od; alpha blocker C: Placebo; alpha blocker	12 wk	I: Age ≥40 yr; use of ABs for LUTS >6 wk; storage symptoms of frequency and urgency (≥8 micturitions and ≥3 urgency episodes per 24 hr); PPBC ≥3 E: PVR >200 mL; poor tolerability of ABs; history of AUR requiring catheterization; history or evidence of clinically significant BOO; prostate cancer; PSA >10 ng/mL; neurological conditions (stroke, multiple sclerosis, spinal cord injury, Parkinson's disease); UTI; >3 episodes UTI in prior 12 mo; history of prostatic, urethral, or bladder surgery; antimuscarinic within 3 wk or 5-ARIs within 6 mo	Mean age: 66 Race: 81% white Baseline IPSS: 19.0
Lee, 2011[30] Korea N=176	T_1: Tolterodine SR 4 mg; doxazosin GITS 4 mg T_2: Doxazosin GITS 4 mg; placebo	4 wk	I: Age ≥50 yr; IPSS ≥14; IPSS-V ≥8; IPSS-S ≥6; QoL-I ≥3; ≥8 micturition per 24 hr; ≥1 micturition with urgency rating 3 per 24 hr; prostate volume ≥20; Qmax ≤15 mL/s; voided volume ≥125 mL E: History of neurogenic bladder dysfunction, prostate cancer, acute or chronic urinary retention, acute or chronic prostatitis within the prior 3 mo; PSA >10 ng/mL; recurrent UTI or bladder stones; previous medication history for BPH; previous surgical intervention related to BPO	Mean age: 61 Race: NR Baseline IPSS: 21.4
Seo, 2011[31] Korea N=56	T: Solifenacin 5 mg qd; tamsulosin 0.2 mg qd C: Tamsulosin 0.2 mg qd	12 wk	I: Age ≥40 yr; concurrent LUTS and ED; IPSS >12; QoL-I >3; IIEF-5 <20 E: Anti-androgens, sex hormone agents, PDE-5s in prior 4 wk; prostate or urethra surgery; urethral stricture; UTI; prostatitis; prostate cancer; bladder cancer; PSA >4 mg/dL; severe renal or hepatic dysfunction; PVR >100 mL	Mean age: 58 Race: NR Baseline IPSS: 17.8
Yamaguchi, 2011[32] Japan N=638	T: Solifenacin 2.5 mg; tamsulosin 0.2 mg T_2: Solifenacin 5 mg; tamsulosin 0.2 mg C: Tamsulosin 0.2 mg; placebo	12 wk	I: Age ≥50 yr; LUTS and residual OAB symptoms; urgency episodes ≥2 per 24 hr; micturitions ≥8 per 24 hr; Qmax ≥5 mL/s; PVR ≥50 mL E: Polyuria (≥3000 mL per 24 hr); urethral stricture; bladder neck stricture; prostate cancer or other malignancy; any disease other than LUTS that would affect voiding; surgery affecting urinary tract function; contraindicates for antimuscarinic or alpha-1 blocker therapy	Mean age: 70 Race: NR Baseline IPSS: 13.5

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Chapple, 2009[33] North America, Asia, Europe, South Africa N=652	T: Tolterodine ER 4 mg; alpha blocker (od 4 hr before bedtime) C: Placebo; alpha blocker (od 4 hr before bedtime)	12 wk	I: Age ≥40 yr; 8 micturitions per 24 hr (including 1 urgency episodes per 24 hr with or without urgency); urinary incontinence moderate bladder-related problems despite use of AB ≥1 mo E: PVR ≤200 mL; history of AUR requiring catheterization; poor detrusor function; presumed clinically significant BOO; prostate cancer; PSA ≥10 ng/mL; UTI; neurological disease or injury; antimuscarinic use in prior 30 d	Mean age: 65 Race: 70% white Baseline IPSS: 18.5
Kaplan, 2009[34] Kaplan, 2013[37] USA N=398	T: Solifenacin 5 mg qd; tamsulosin 0.4 mg qd C: Tamsulosin 0.4 mg qd; placebo	12 wk	I: Age >45 yr; residual OAB symptoms (>8 micturitions and >1 urgency episodes per 24 hr); history of LUTS >3 mo; IPSS ≥13; PPBC ≥3; PVR ≤200 mL; PFR ≥5 mL/s E: Antimuscarinic therapy or participation in trials involving investigational drug in prior 30 d; urinary or gastric retention; ≥3 recurrent UTI episodes in prior 12 mo; prior or planned prostate surgery; 5-ARIs use with prior 3 mo; PSA >10 ng/mL	Mean age: 65 Race: 84% white Baseline IPSS: 16.9
MacDiarmid, 2008[35] USA N=420	T: Oxybutynin 10 mg od; tamsulosin 0.4 mg od C: Tamsulosin 0.4 mg od; placebo	12 wk	I: Age ≥45 yr; LUTS (IPSS ≥13, IPSS-S ≥8); PFR ≥4 mL/s; void volumes ≥125 mL; PVR ≤200 mL on ≥2 occasions E: History of urinary retention, bladder or prostate cancer, PSA ≥4 ng/mL (unless prostate cancer ruled out), angle-closure glaucoma, prostate surgery, or serious medical comorbidity; current medications for LUTS (α1-blockers other than tamsulosin, or 5α-reductase agents initiated within the past 4 months, and antimuscarinic agents)	Mean age: 63 Race: 90% white Baseline IPSS: 20.4
Kaplan, 2006[36] Kaplan, 2008[38] Roehrborn, 2008[39] Roehrborn, 2009[40] USA N=879	T: Tolterodine ER 4 mg T_2: Tolterodine ER 4 mg; tamsulosin 0.4 mg C_1: Placebo C_2: Tamsulosin 0.4 mg	12 wk	I: Age ≥40 yr; IPSS ≥12; IPSS QoL ≥3; OAB (≥8 voids/24 hr with urgency, ≥3 episodes/24 hr with or without urgency); reported 'some moderate problems' on PPBC E: PVR >200 mL; Qmax <5 mL/s; PSA >10 ng/mL and risk of prostate cancer	Mean age: 62 Race: 81% white Baseline IPSS: 19.9

AB=alpha blocker; ARI=alpha-reductase inhibitor; AUR=acute urinary retention; bid=twice daily; BOO=bladder outlet obstruction; BOOI=bladder outlet obstruction index; BPH=benign prostatic hyperplasia; BPO=benign prostate obstruction; cm^3=cubic centimeters; d=days; C=comparator group; C_1=comparator group 1; C_2=comparator group 2; dL=deciliters; E=exclusion criteria; ED=erectile dysfunction; g=grams; HbA1c= glycated haemoglobin; hr=hour; HRQL=health-related quality of life; I=inclusion criteria; IIEF-5=5-item International Index of Erectile Function; IPSS=International Prostate Symptom Score-Total; IPSS-S=International Prostate Symptom Score-Storage Subscale; IPSS-V=International Prostate Symptom Score-Voiding Subscale; LUTS=lower urinary tract symptoms; mg=milligrams; min=minute; mL=milliliters; ng=nanograms; NR=not reported; OAB=overactive bladder; PFR=urine peak flow rate; PPBC=patient perception of bladder condition questionnaire; PPIUS=Patient Perception of Intensity of Urgency Scale; PSA=prostate-specific antigen; PVR=postvoid residual urine; qd=daily; Qmax=maximum urinary flow rate; QoL=quality of life; QoL-I=International Prostate Symptom Score-QoL Item; s=second; T=treatment group; T_1=treatment group 1; T_2=treatment group 2; UTI=urinary tract infection; wk=weeks; yr=years

Table E3. Strength of evidence assessments: tolterodine

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Tolterodine 4 mg vs. placebo	I-PSS score, *mean change from baseline*	1 (419)	WMD = -0.70 [-1.88, 0.48]	Low	Direct	Precise	Unknown	Undetected[a]	Low
	BII, *mean change from baseline*	0							Insufficient
	I-PSS QoL, *mean change from baseline*	1 (419)	WMD = -0.10 [-0.40, 0.20]	Low	Direct	Precise	Unknown	Undetected[a]	Low
	Overall withdrawals	1 (439)	RR 0.84 [0.53, 1.34]	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Withdrawals due to adverse effects	1 (439)	RR = 0.73 [0.24, 2.27]	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Participants with ≥1 adverse effect	0							Insufficient
Tolterodine, 4 mg plus alpha-blocker vs. placebo	IPSS/AUA-SI , *mean change from baseline*	1 (416)	WMD=-1.80 [-2.92, --0.68]	Low	Direct	Precise	Unknown	Undetected[a]	Low
	IPSS QoL, *mean change from baseline*	1 (418)	WMD=-0.40 [-0.66, -0.14]	Low	Direct	Precise	Unknown	Undetected[a]	Low
	AUR	1 (445)	OR=0.65 [0.11, 3.80]	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Overall withdrawals	1 (447)	RR=0.99 [0.64, 1.53]	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Withdrawals due to adverse effects	1 (447)	RR=2.82 [1.22, 6.53]	Low	Direct	Precise	Unknown	Undetected[a]	Low
Tolterodine, 4 mg plus alpha-blocker vs. alpha-blocker	Responders	1 (70)	RR = 2.7; 95% [1.55, 4.70]	High	Direct	Precise	Unknown	Undetected[a]	Insufficient
	IPSS score, *mean change from baseline*	4 (1249)	WMD = -0.19 [-0.74, 0.35]	Low-Moderate	Direct	Precise	Consistent	Undetected[a]	Moderate
	IPSS QoL, mean change from baseline	3 (1182)	WMD= -0.34 [-0.73, 0.06]	Low	Direct	Imprecise	Inconsistent	Undetected[a]	Low
	AUR	3 (1268)	OR= 2.69 [0.67, 10.80]	Low	Indirect	Imprecise	Consistent	Undetected[a]	Insufficient
	Overall withdrawals	3 (1268)	RR= 1.11 [0.79, 1.56]	Low	Direct	Imprecise	Consistent	Undetected[a]	Moderate
	Withdrawals due to adverse effects	3 (1268)	RR= 2.17 [1.21, 3.88]	Low	Direct	Precise	Consistent	Undetected[a]	High
	Participants with ≥1 adverse effect	1 (652)	RR= 1.26 [1.00, 1.58]	Low	Direct	Imprecise	Unknown	Undetected[a]	Low
Tolterodine 4 mg vs.	IPSS score, *mean change from*	1 (137)	MD = -2.4 [NA]	High	Direct	Imprecise	Unknown	Undetected[a]	Insufficient

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
alpha-blocker and or 5ARI	*baseline*								
	IPSS QoL, mean change from baseline	1 (137)	MD = -0.1 [NA]	High	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
Tolterodine 4 mg vs. tamsulosin 0.4 mg	I-PSS score, *mean change from baseline*	1 (403)	MD = 0.90 [-0.46, 2.26]	Low	Direct	Precise	Unknown	Undetected[a]	Insufficient
	I-PSS QoL, *mean change from baseline*	1(403)	MD = -0.10 [-0.21, 0.41]	Low	Direct	Precise	Unknown	Undetected[a]	Low
	Overall withdrawals	1 (432)	RR 0.96 [0.59, 1.55]	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Withdrawals due to adverse effects	1 (439)	RR = 0.71 [0.23, 2.20]	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Participants with ≥1 adverse effect	0							Insufficient
Tolterodine 4 mg vs. doxazosin 4 mg	I-PSS score, *mean change from baseline*	1 (89)	MD = -0.20 [-2.32, 1.92]	High	Direct	Precise	Unknown	Undetected[a]	Insufficient
	I-PSS QoL, *mean change from baseline*	1 (89)	MD = -0.20 [-0.61, 0.21]	High	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Overall withdrawals	1 (202)	RR = 0.83 [0.47, 1.45]	High	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Withdrawals due to adverse effects	1 (202)	RR = 0.65 [0.15, 2.84]	High	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Participants with ≥1 adverse effect	0							Insufficient

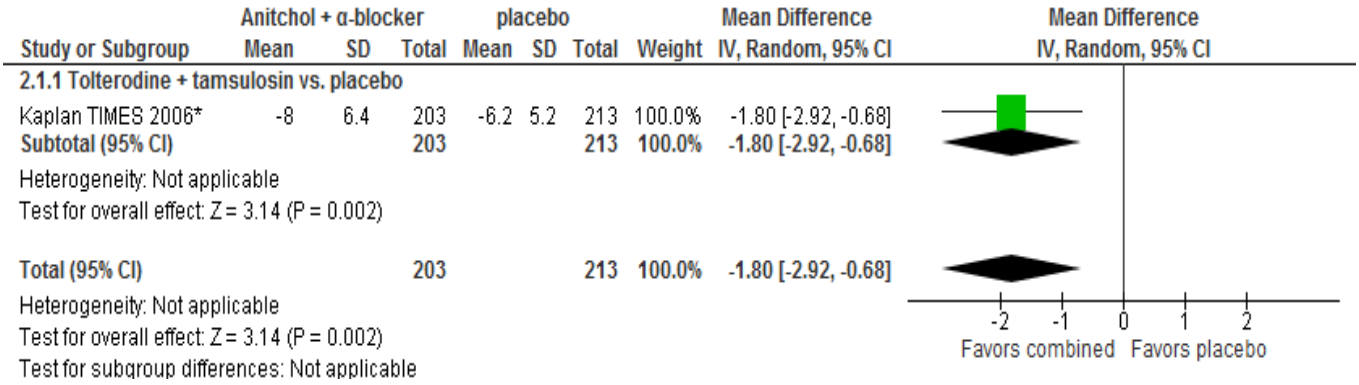
[a] We searched and screened results from clinicaltrials.gov. We identified one eligible tolterodine trial with a completion date of November 2015. We did not considered the lack of publication bias of this trial an indication of publication bias.

ARD=absolute risk difference; ARR=absolute risk reduction; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

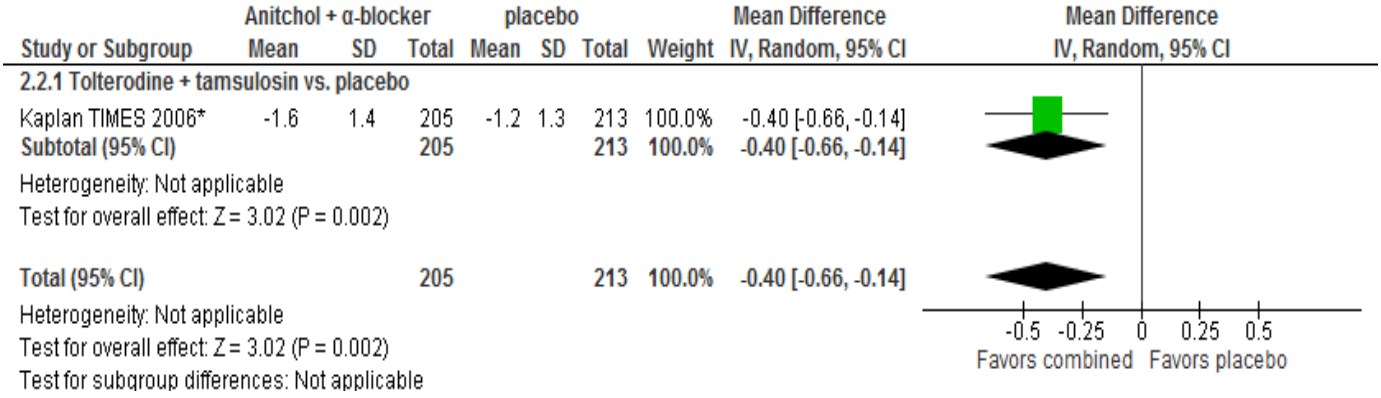
Analyses for Combined Tolterodine + α-Blocker Versus Placebo

Figure E1. IPSS scores, mean change from baseline



* Indicates data was extracted and estimated from graph

Figure E2. IPSS QoL scores, mean change from baseline



*Indicates data was extracted and estimated from graph

Figure E3. Urinary retention

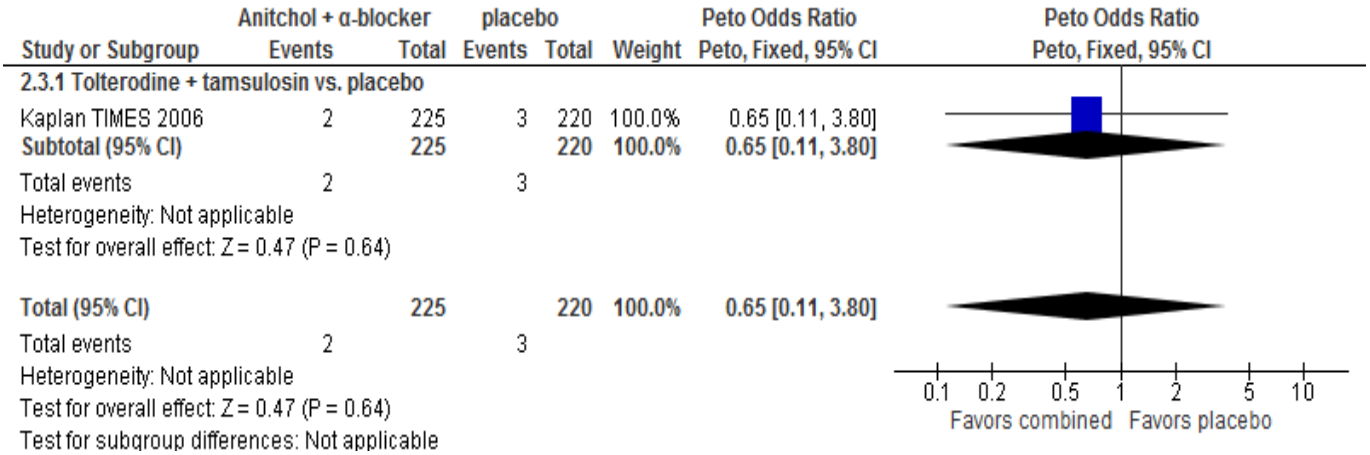


Figure E4. Withdrawal for any reason

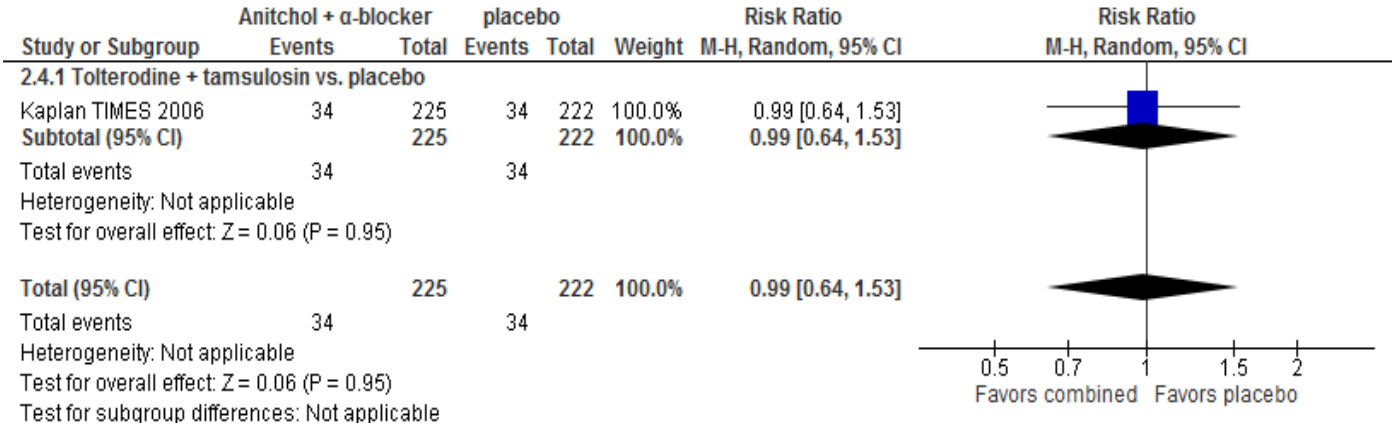
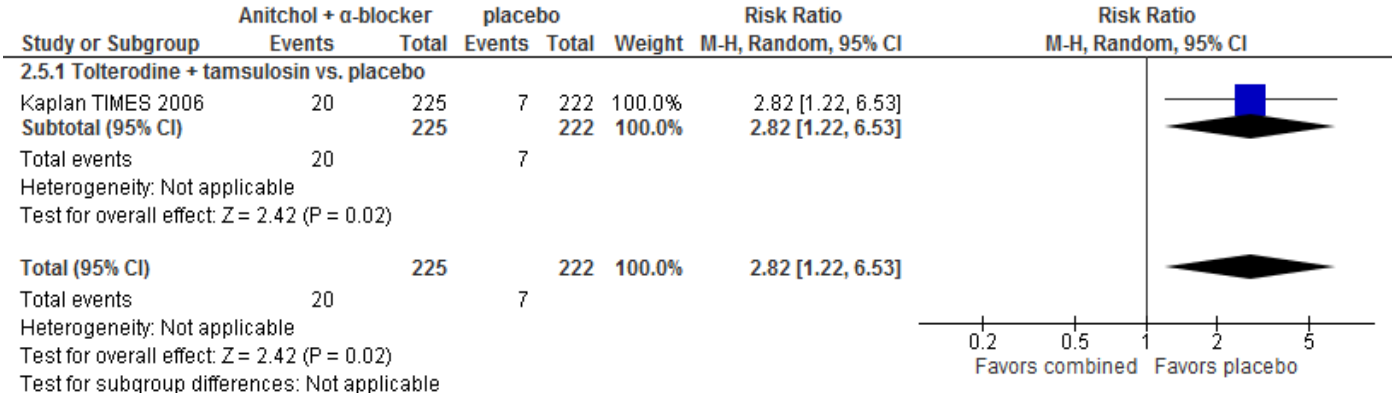


Figure E5. Withdrawal due to an AE



Analyses for Combined Tolterodine + α-Blocker Versus α-Blocker Monotherapy

Figure E6. IPSS: >3 improvement from baseline

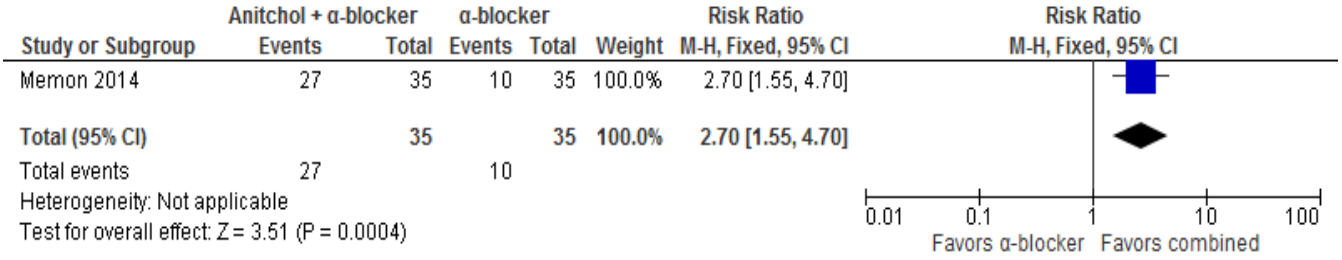
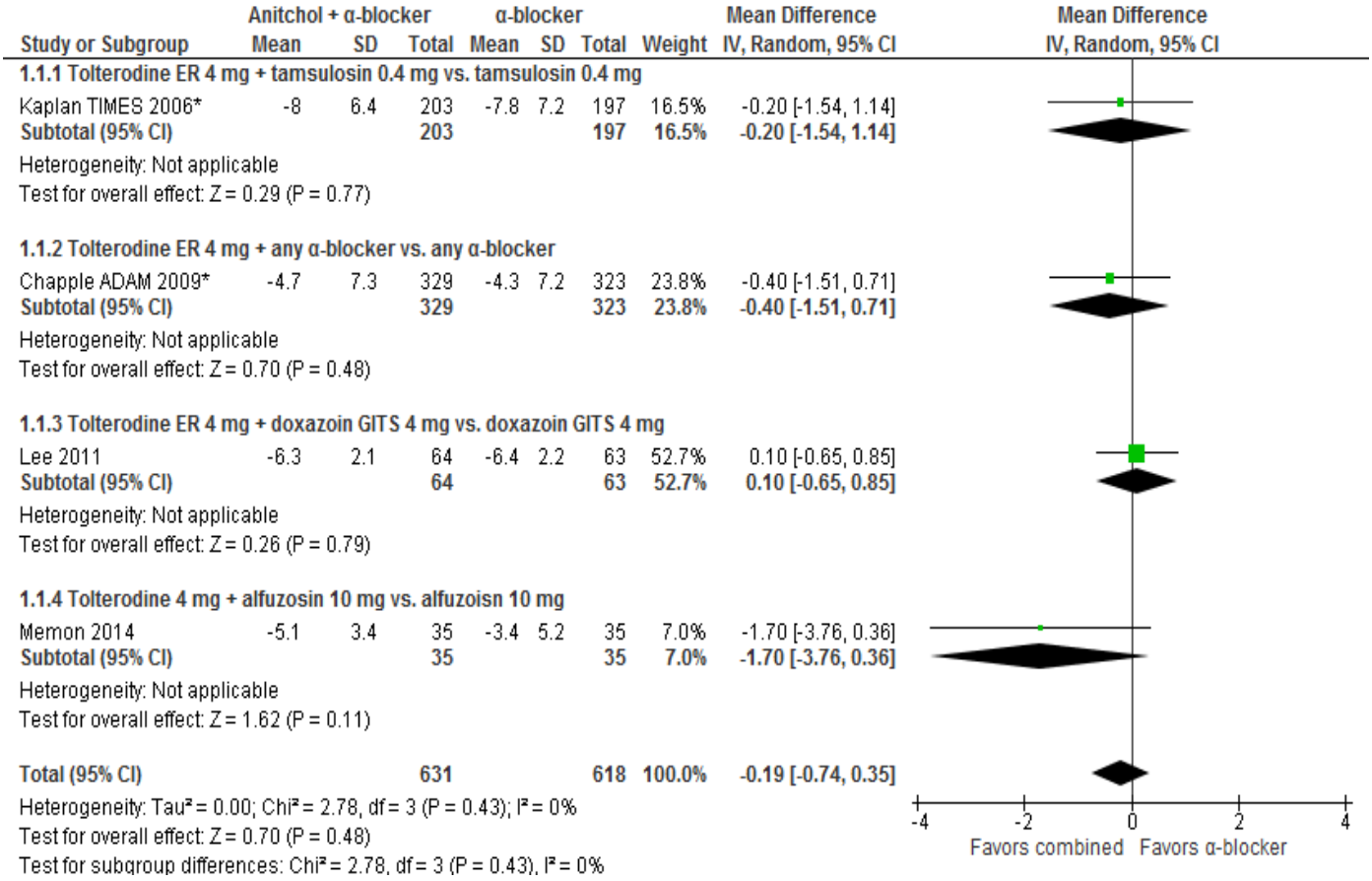
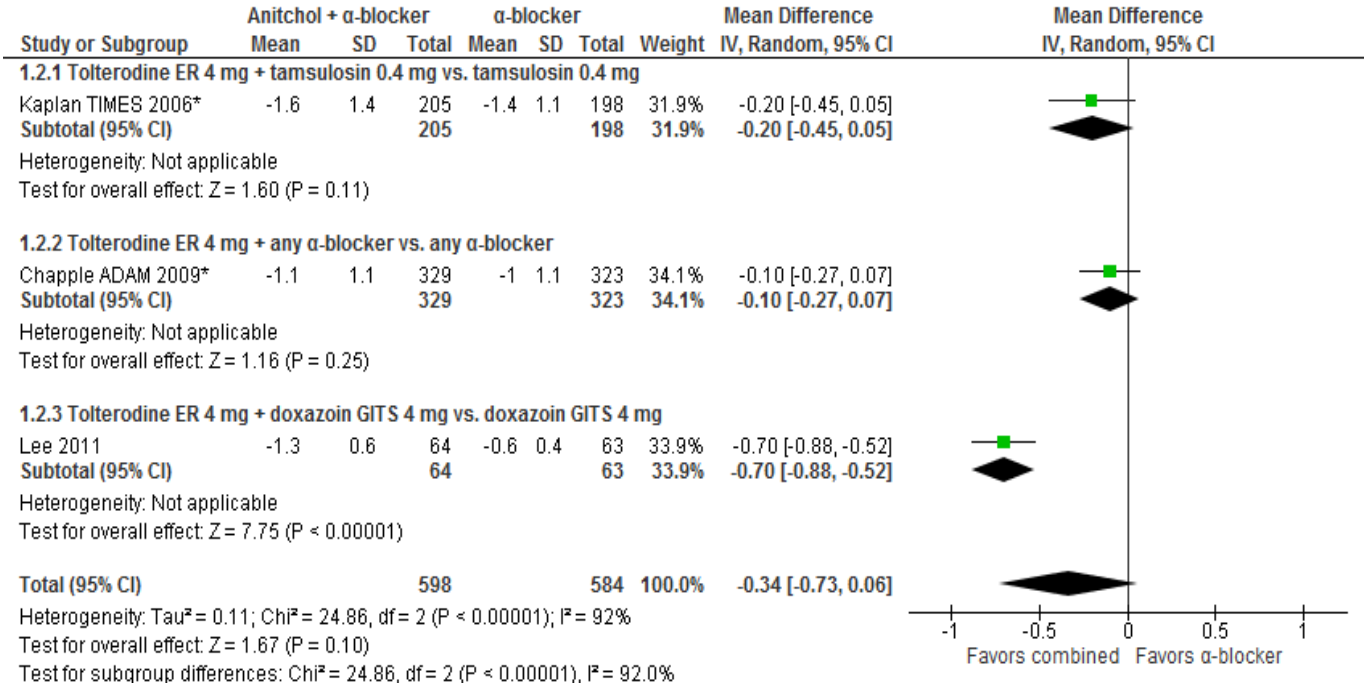


Figure E7. IPSS scores, mean change from baseline



* Indicates data was extracted and estimated from graph

Figure E8. IPSS QoL scores, mean change from baseline



* Indicates data was extracted and estimated from graph

Figure E9. Urinary retention

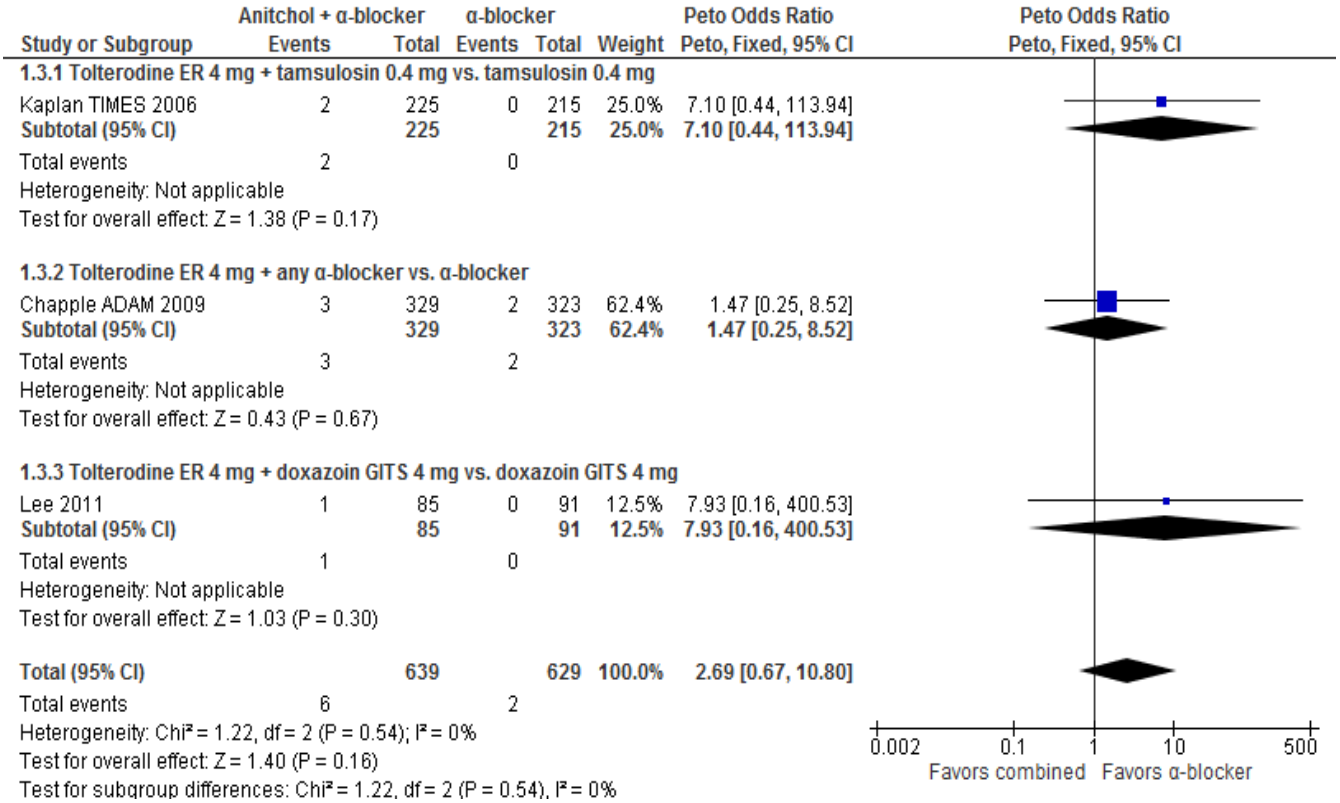


Figure E10. Catheterization required

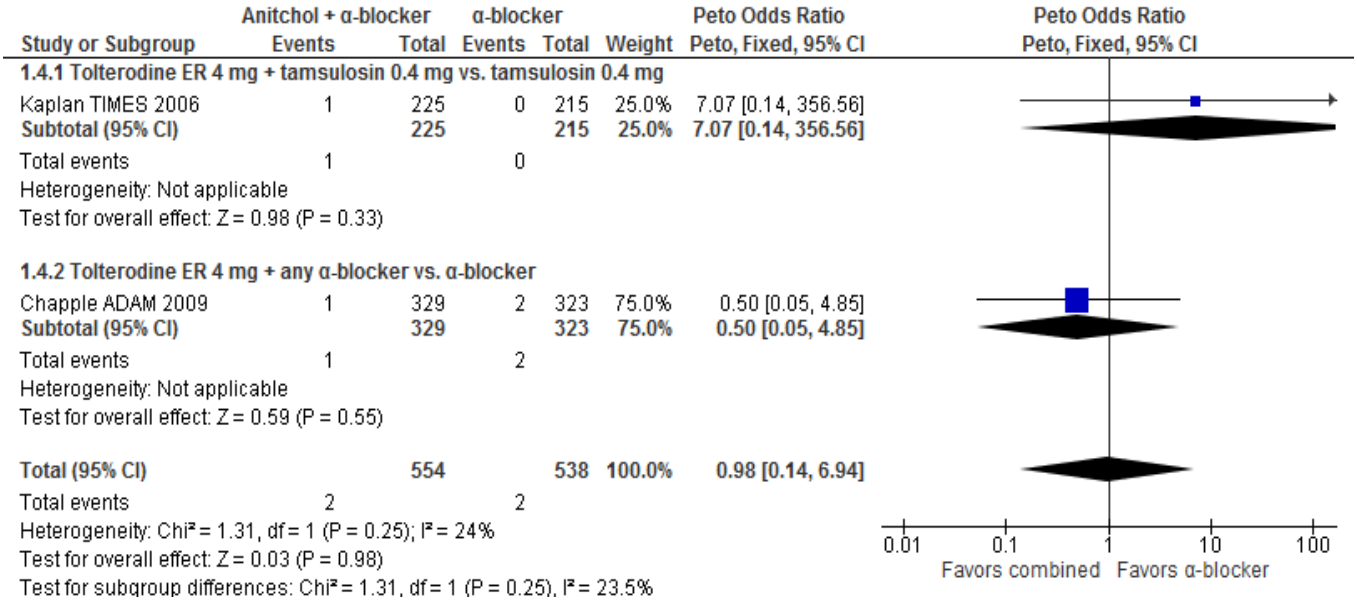


Figure E11. Withdrawal for any reason

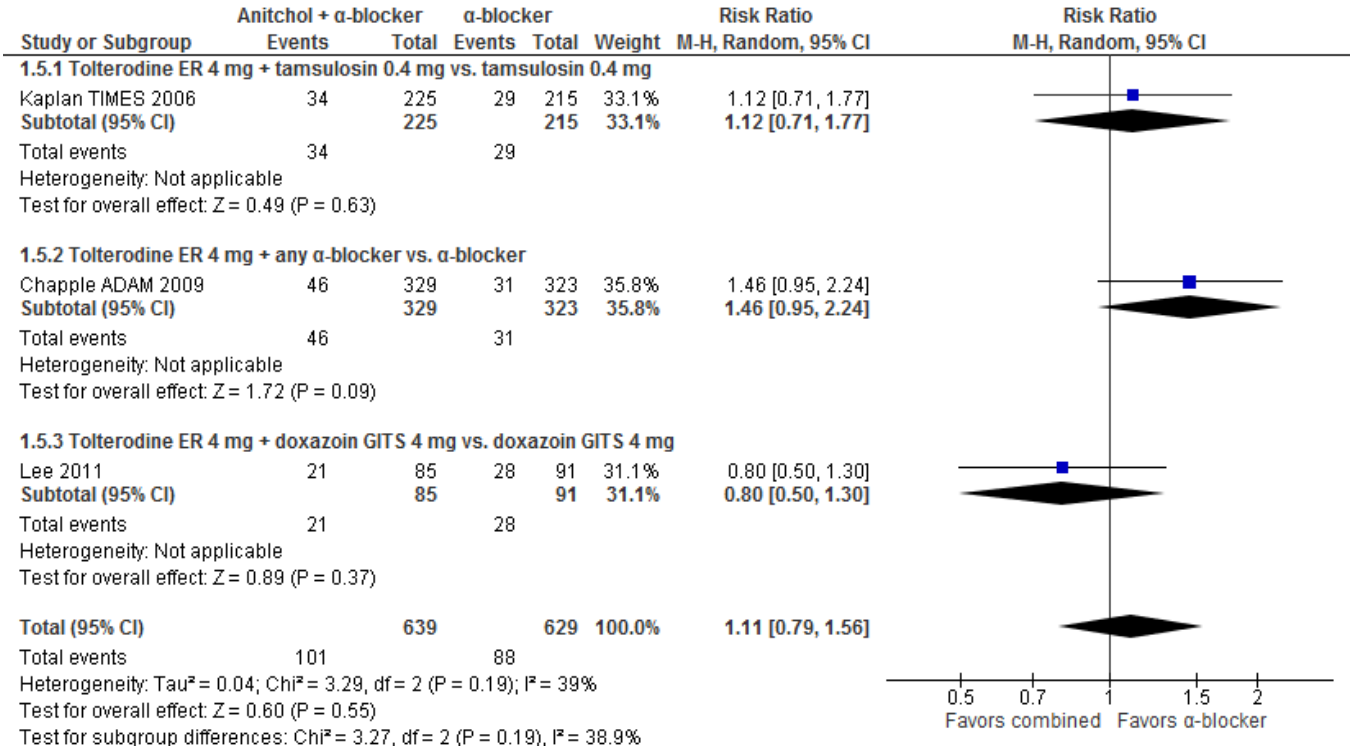


Figure E12. Withdrawal due to an AE

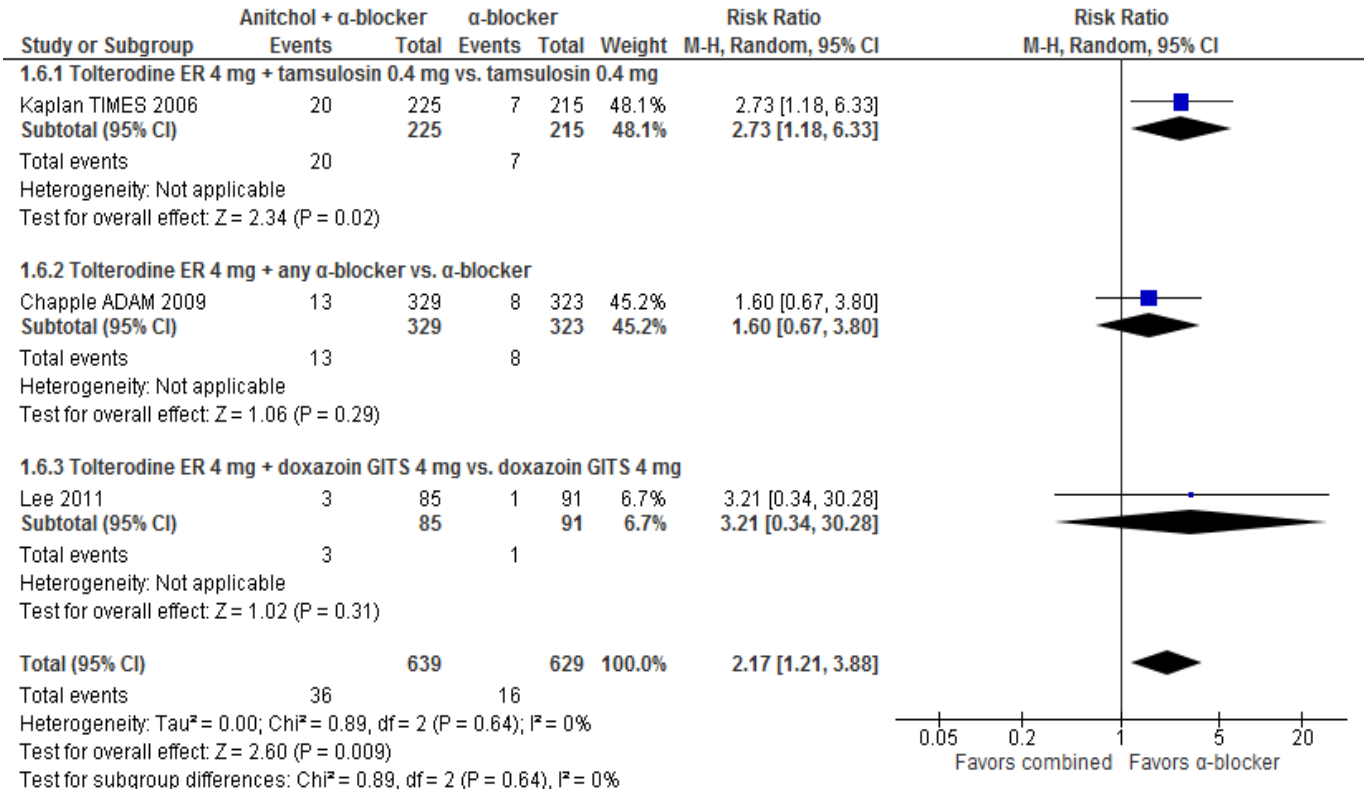


Figure E13. Patients with ≥1 adverse effect

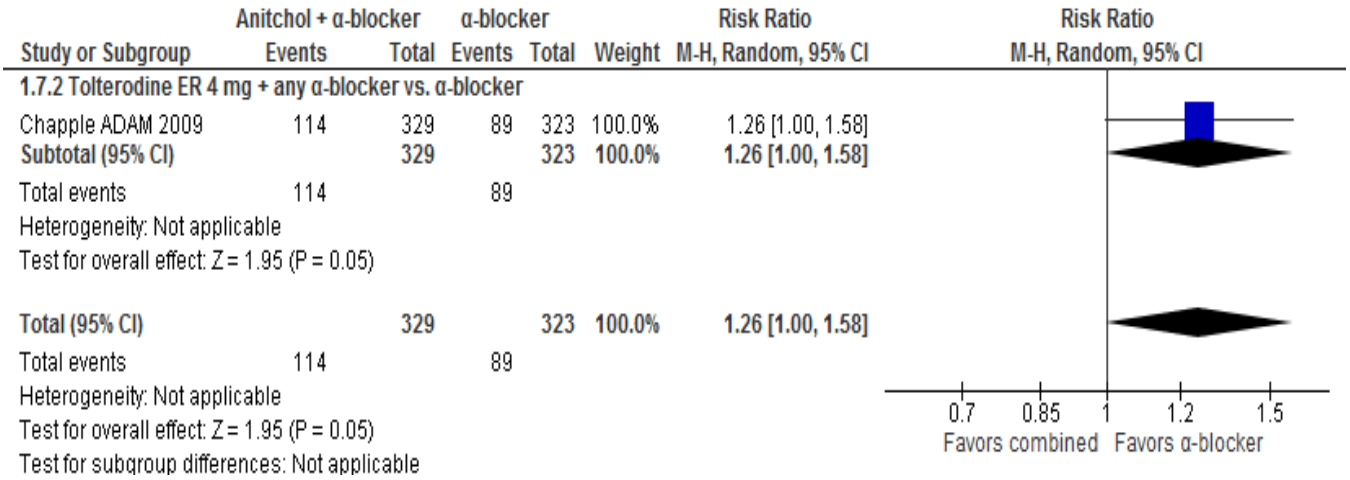


Figure E14. Dry mouth

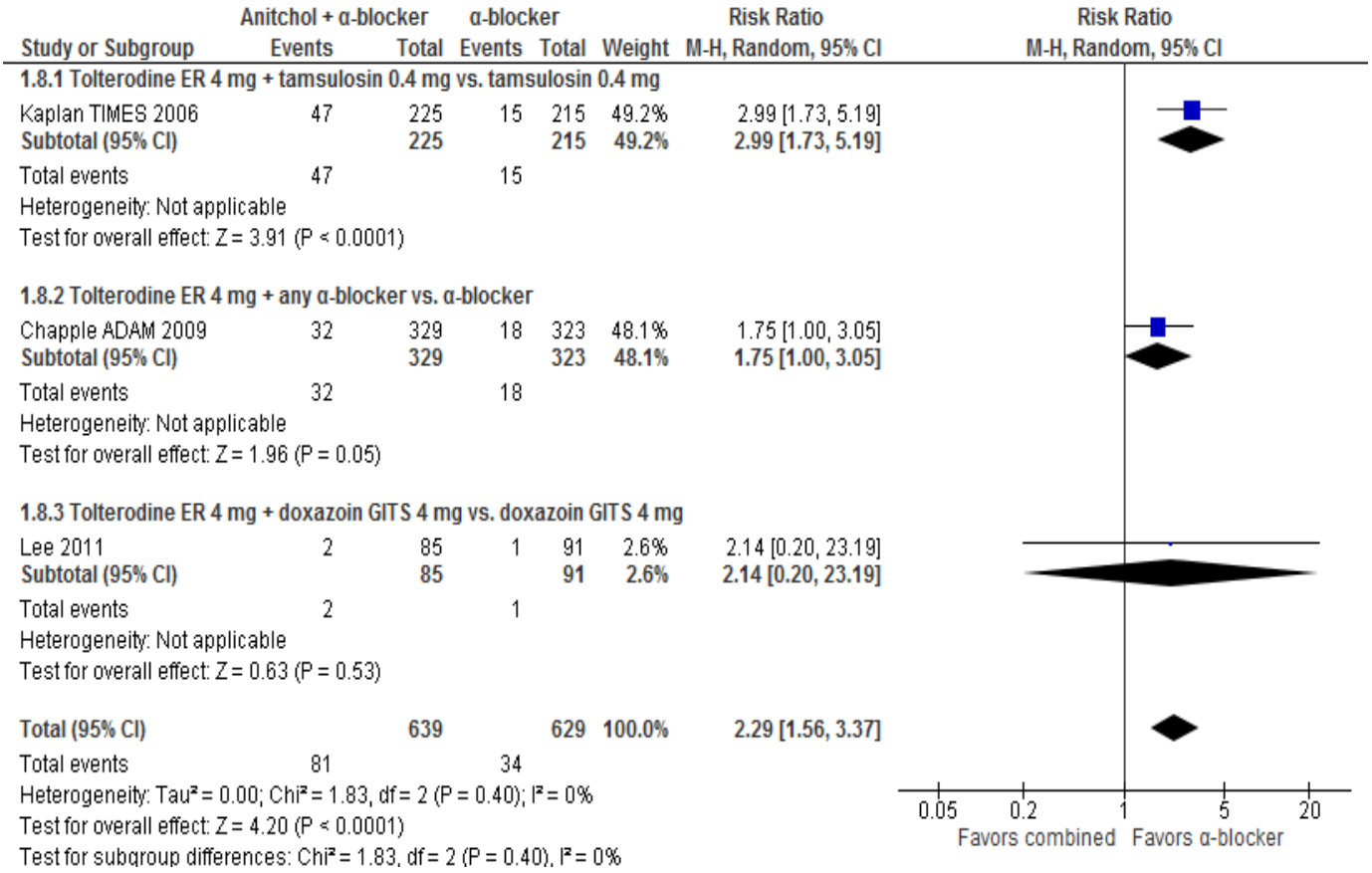


Table E4. Strength of evidence assessments: solifenacin

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Solifenacin 6 mg vs. placebo	I-PSS score, *mean change from baseline*	1 (215)	MD = -0.30 [-1.74, 2.34]	Moderate	Direct	Precise	Unknown	Undetected[a]	Low
	BII, *mean change from baseline*	NR			Direct			Undetected[a]	Insufficient
	I-PSS QoL, *mean change from baseline*	NR			Direct			Undetected[a]	Insufficient
	Overall withdrawals	1 (222)	RR = 1.95 [0.64, 5.92]	Moderate	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Withdrawals due to adverse effects	1 (222)	RR = 4.97 [0.26, 95.06]	Moderate	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Participants with ≥1 adverse effect	1 (221)	RR = 1.19 [0.61, 2.31]	Moderate	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
Solifenacin, 6 mg plus alpha-blocker vs. placebo	IPSS/AUA-SI , *mean change from baseline*	3 (1023)	WMD= -1.50 [-2.30, -0.70]	Low	Direct	Imrecise	Consistent	Undetected[a]	Moderate
	IPSS QoL, *mean change from baseline*	1 (629)	WMD= -0.40 [-0.70, -0.10]	Low	Direct	Precise	Unknown	Undetected[a]	Low
	Overall withdrawals	3 (1857)	RR= 1.20 [0.76, 1.89]	Low	Direct	Imprecise	Unknown	Undetected[a]	Low
	Withdrawals due to adverse effects	3 (1857)	RR= 2.17 [1.04, 4.55]	Low	Direct	Precise	Unknown	Undetected[a]	Moderate
	Participants with ≥1 adverse effect	3 (1848)	RR = 1.24 [1.04 to 1.47] ARD = 0.06 [0.02 to 0.10] NNH = 17	Low	Direct	Precise	Unknown	Undetected[a]	High
Solifenacin, 5 or 6 mg plus alpha-blocker vs. alpha-blocker	IPSS score, mean change from baseline	6 (1948)	WMD=-0.29 [-0.74, 0.16]	Low	Direct	Precise	Consistent	Undetected[a]	Moderate
	IPSS QoL, *mean change from baseline*	4 (1225)	WMD=-0.18 [-0.34, -0.02]	Low	Direct	Precise	Consistent	Undetected[a]	Moderate
	AUR	4 (2531)	RR=3.75 [1.11, 12.69]	Low	Direct	Precise	Consistent	Undetected[a]	Low
	Overall withdrawals	7 (3147)	RR=1.02 [0.78, 1.33]	Low-	Direct	Imprecise	Consistent	Undetected[a]	Moderate

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
				Moderate					
	Withdrawals due to adverse effects	5 (2900)	RR=1.27 [0.84, 1.95]	Low	Direct	Imprecise	Consistent	Undetected[a]	Moderate
	Participants with ≥1 adverse effect	5 (2918)	RR=1.21 [1.08, 1.36]	Low	Direct	Precise	Consistent	Undetected[a]	High

[a] We searched and screened results from clinicaltrials.gov. We identified for two eligible solifenacin trials; both have been published and included in our review. We did not detect publication bias.

ARD=absolute risk difference; ARR=absolute risk reduction; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

Analyses for Combined Solifenacin + α-Blocker Versus Placebo

Figure E15. IPSS scores, mean change from baseline based on dose

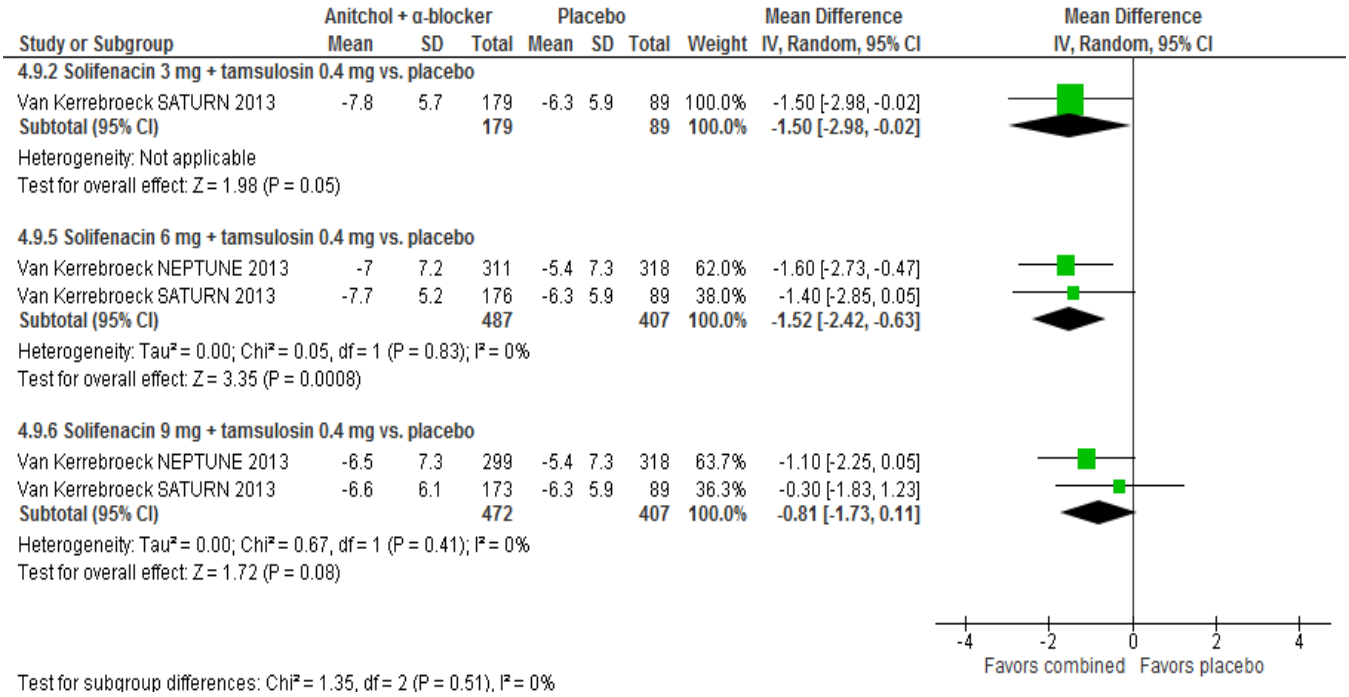


Figure E16. IPSS QoL scores, mean change from baseline

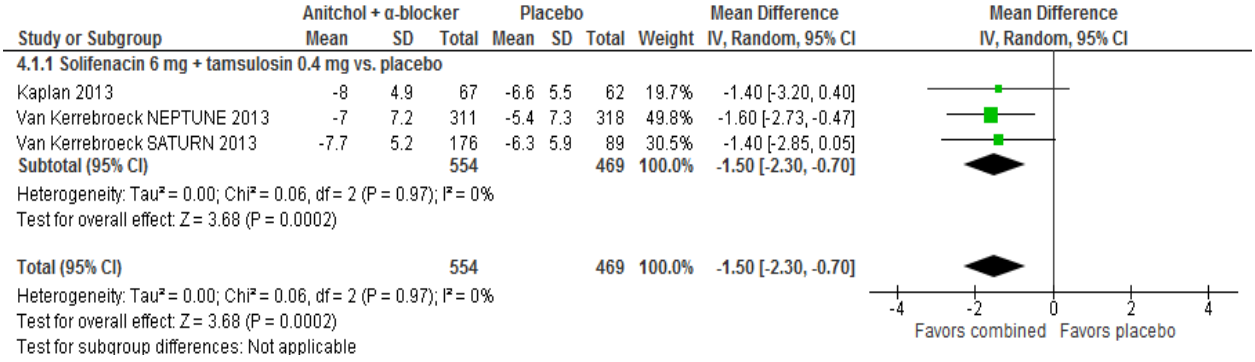


Figure E17. Urinary retention

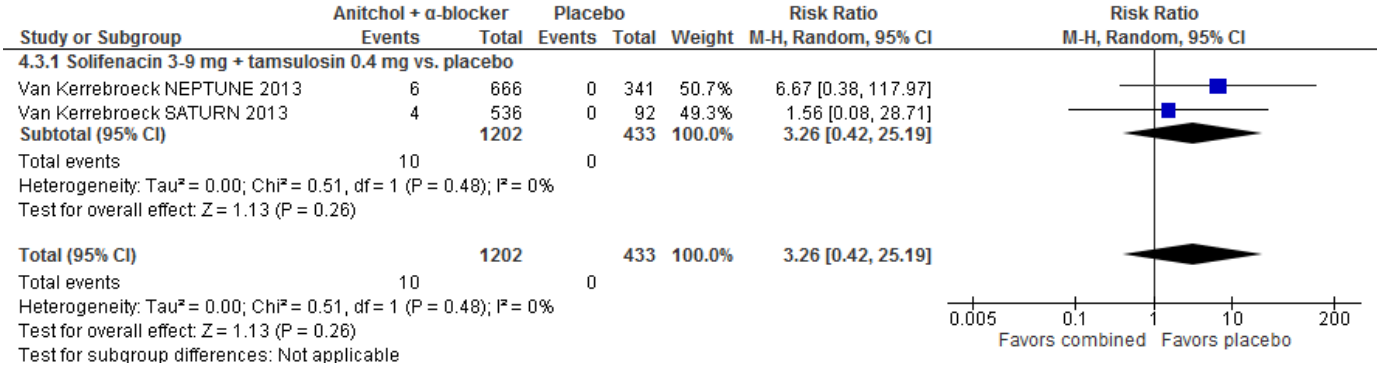


Figure E18. Withdrawal for any reason

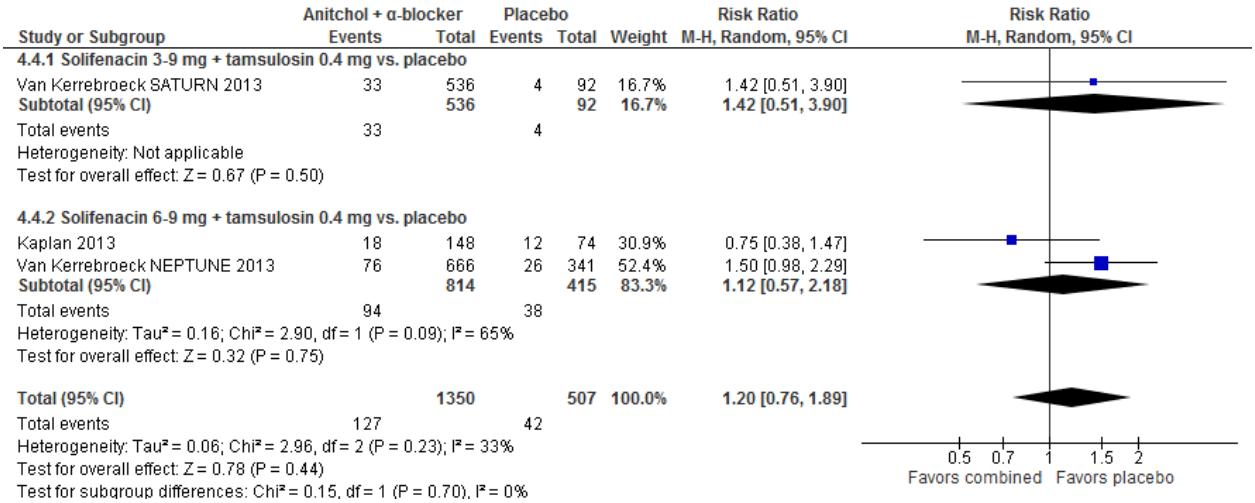


Figure E19. Withdrawal due to an AE

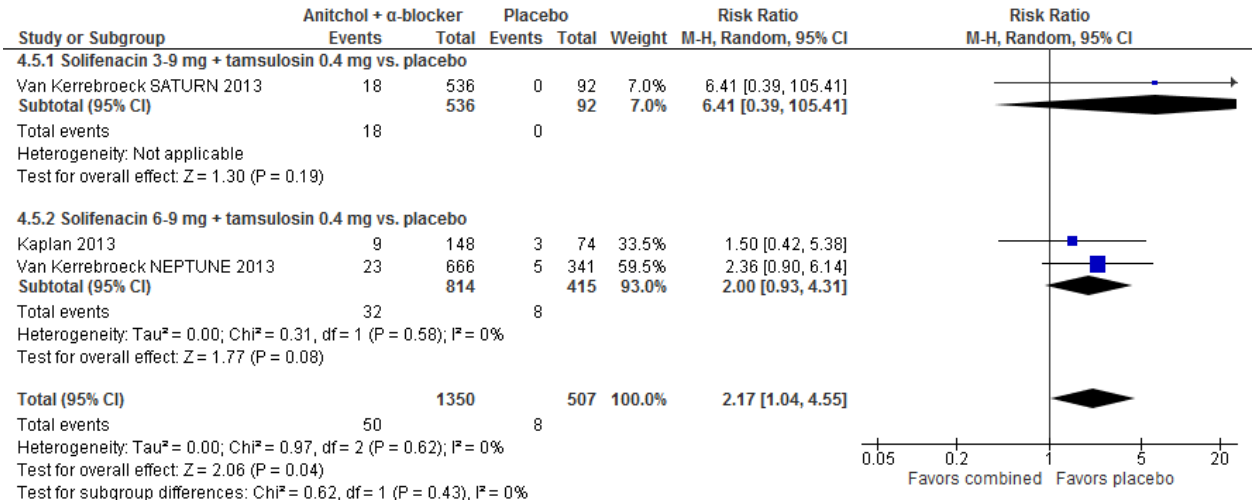
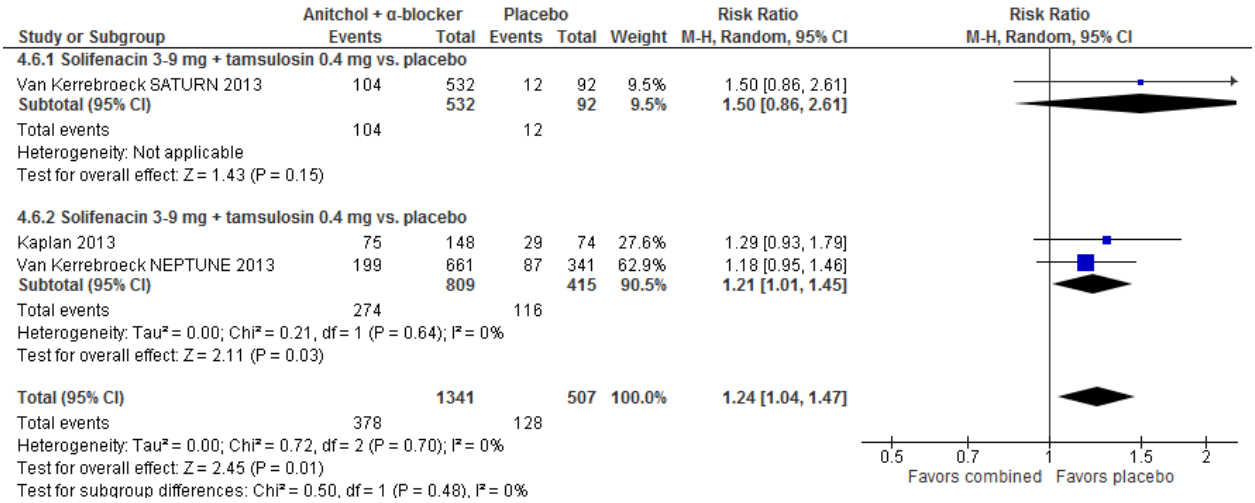


Figure E20. Patients with ≥1 adverse effect



Analyses for Combined Solifenacin + α-Blocker Versus α-Blocker Monotherapy

Figure E21. IPSS scores, mean change from baseline (*for solifenacin 5-6 mg doses*)

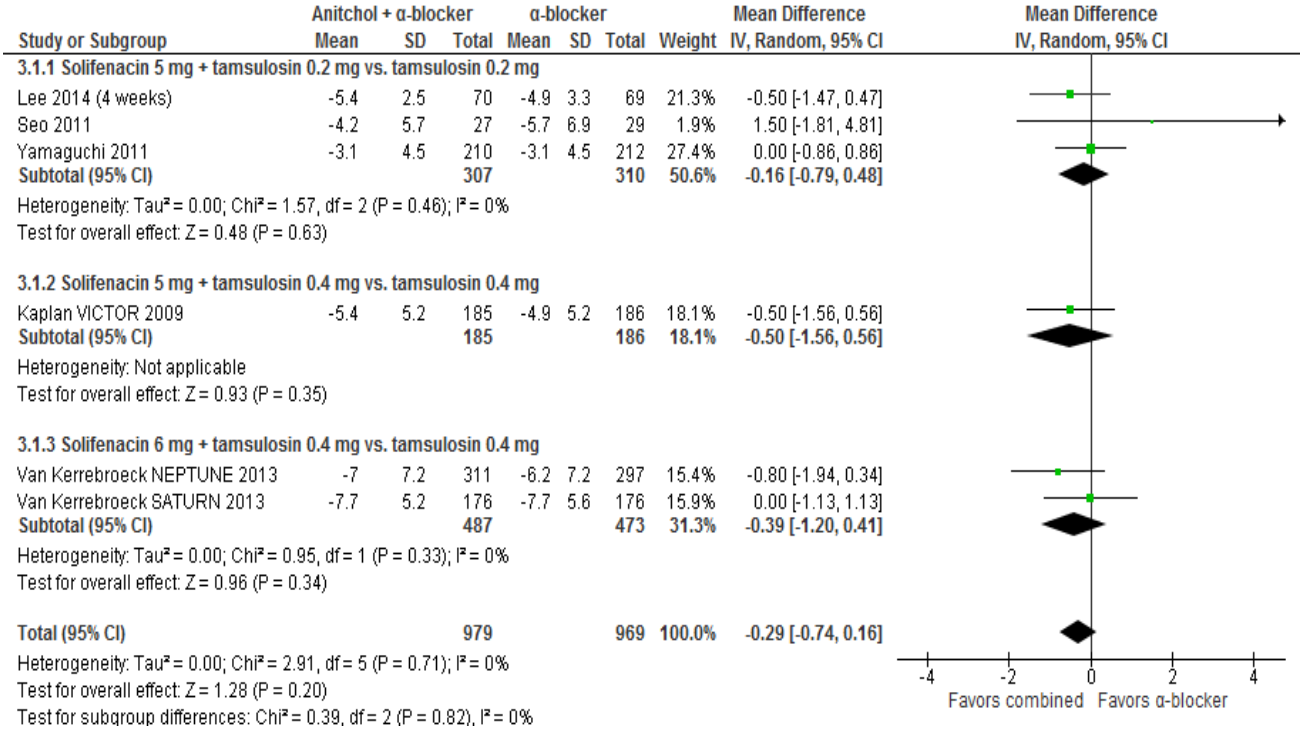


Figure E22. IPSS scores, mean change from baseline based on dose

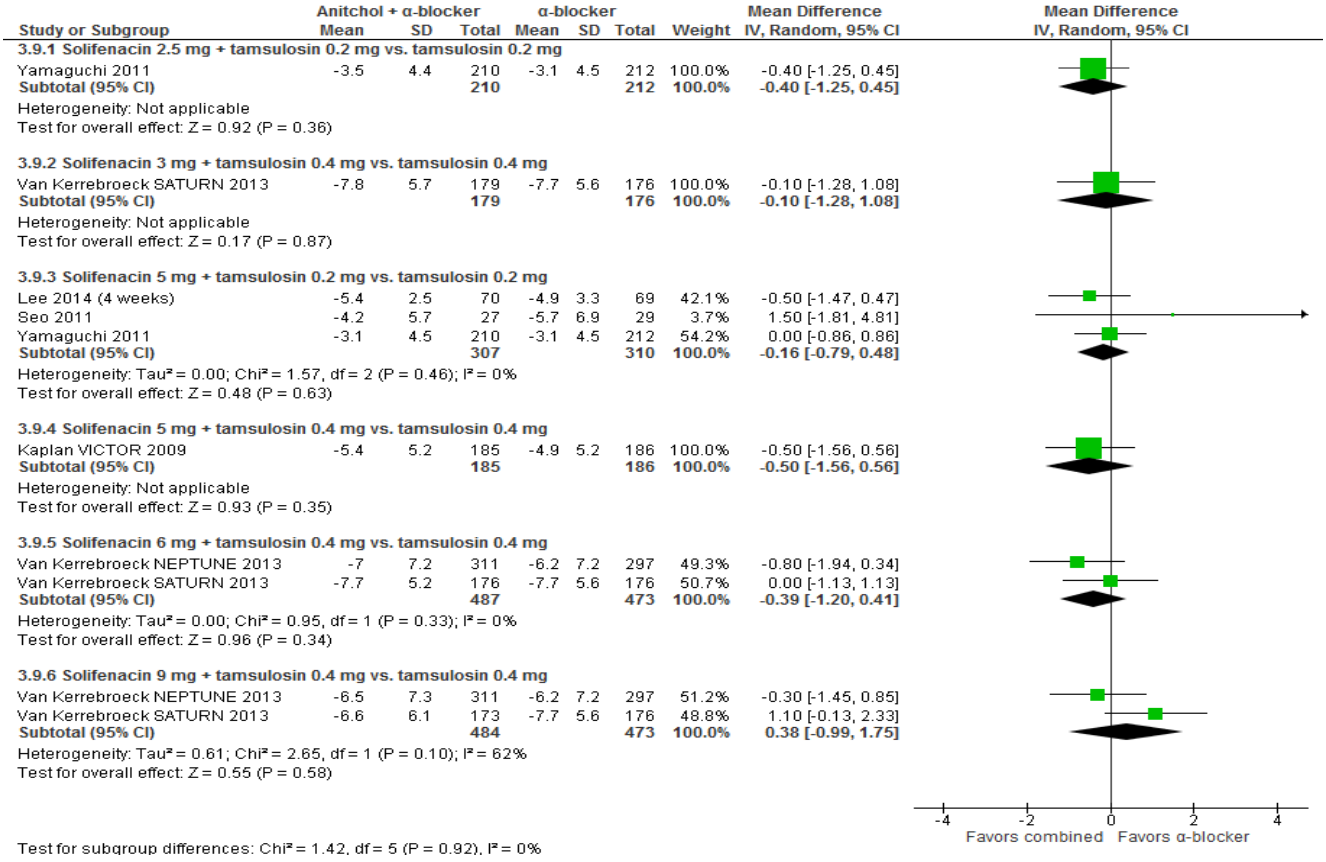


Figure E23. IPSS QoL scores, mean change from baseline

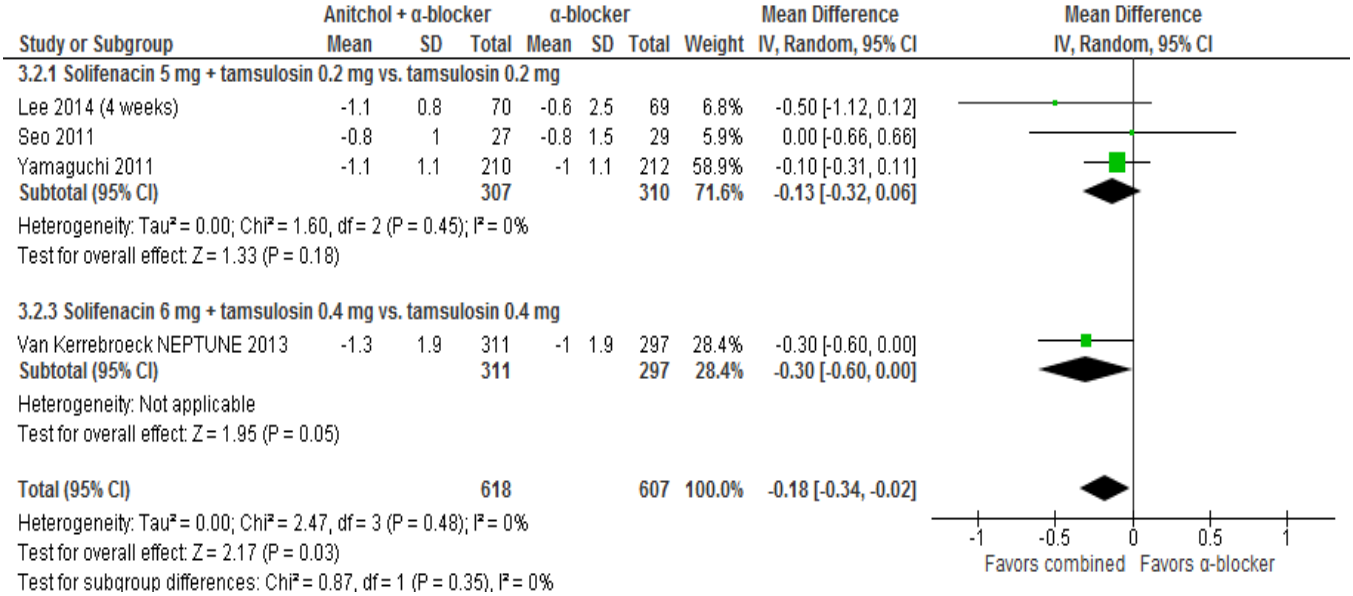


Figure E24. Urinary retention

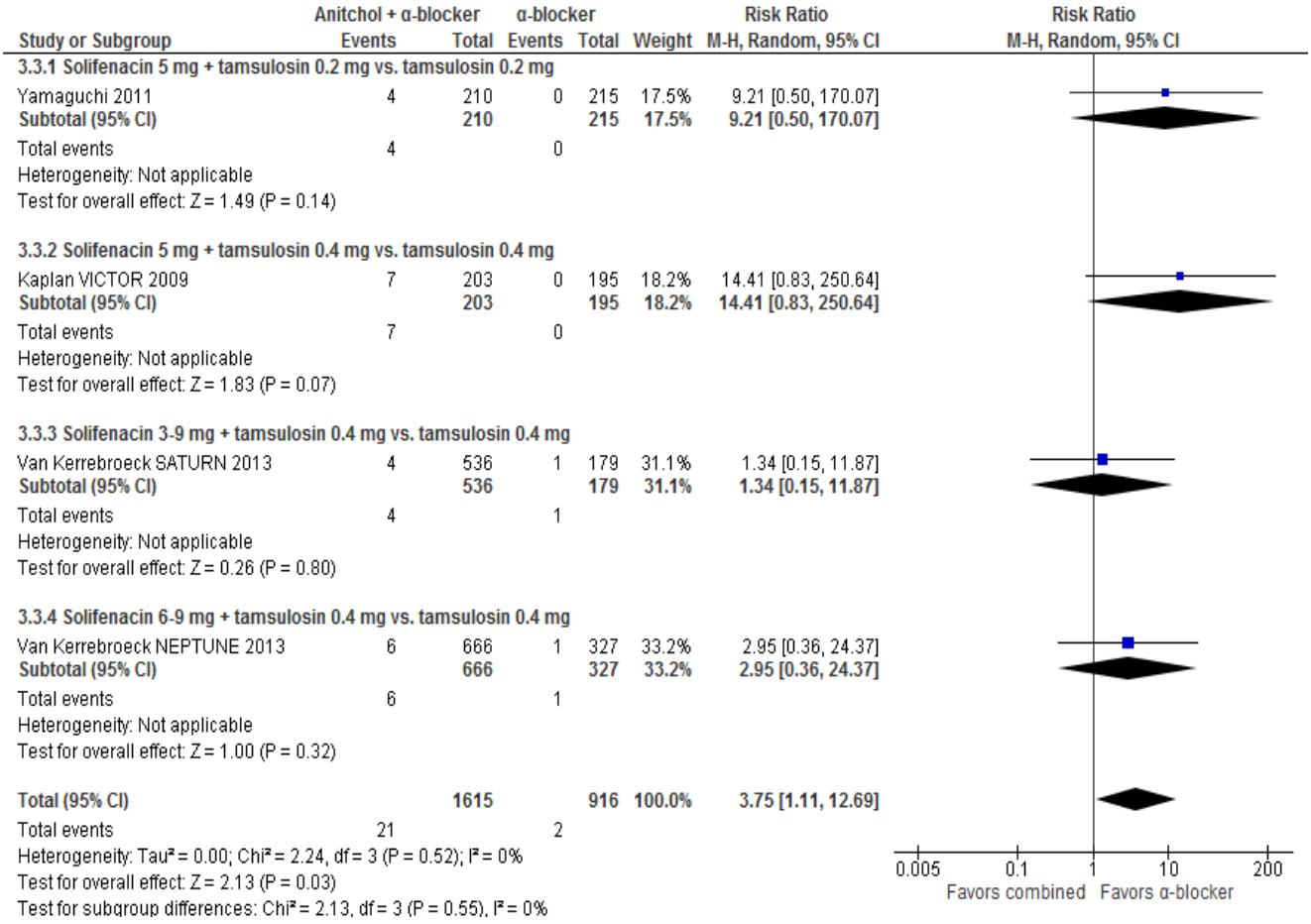


Figure E25. Withdrawal for any reason

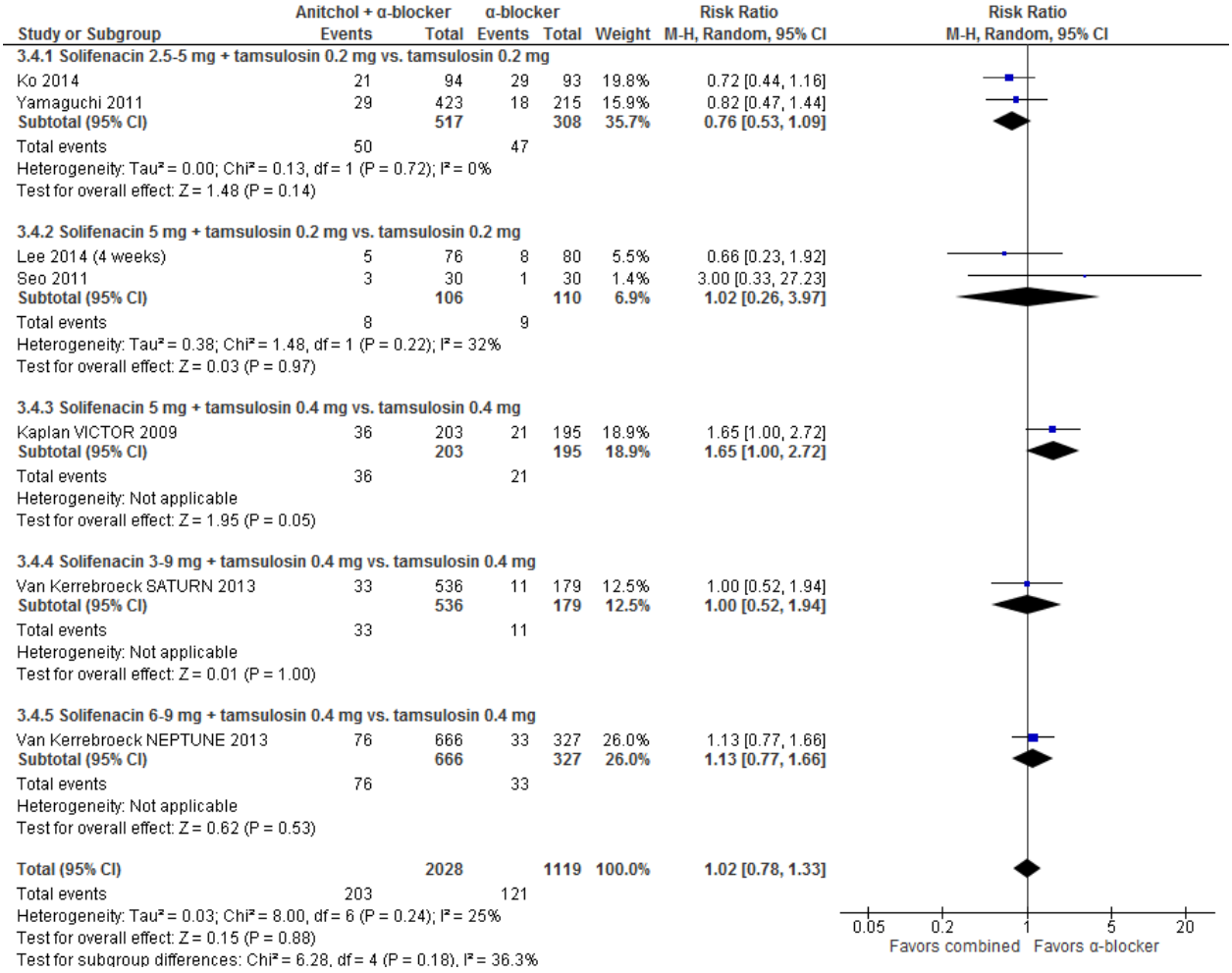


Figure E26. Withdrawal due to an AE

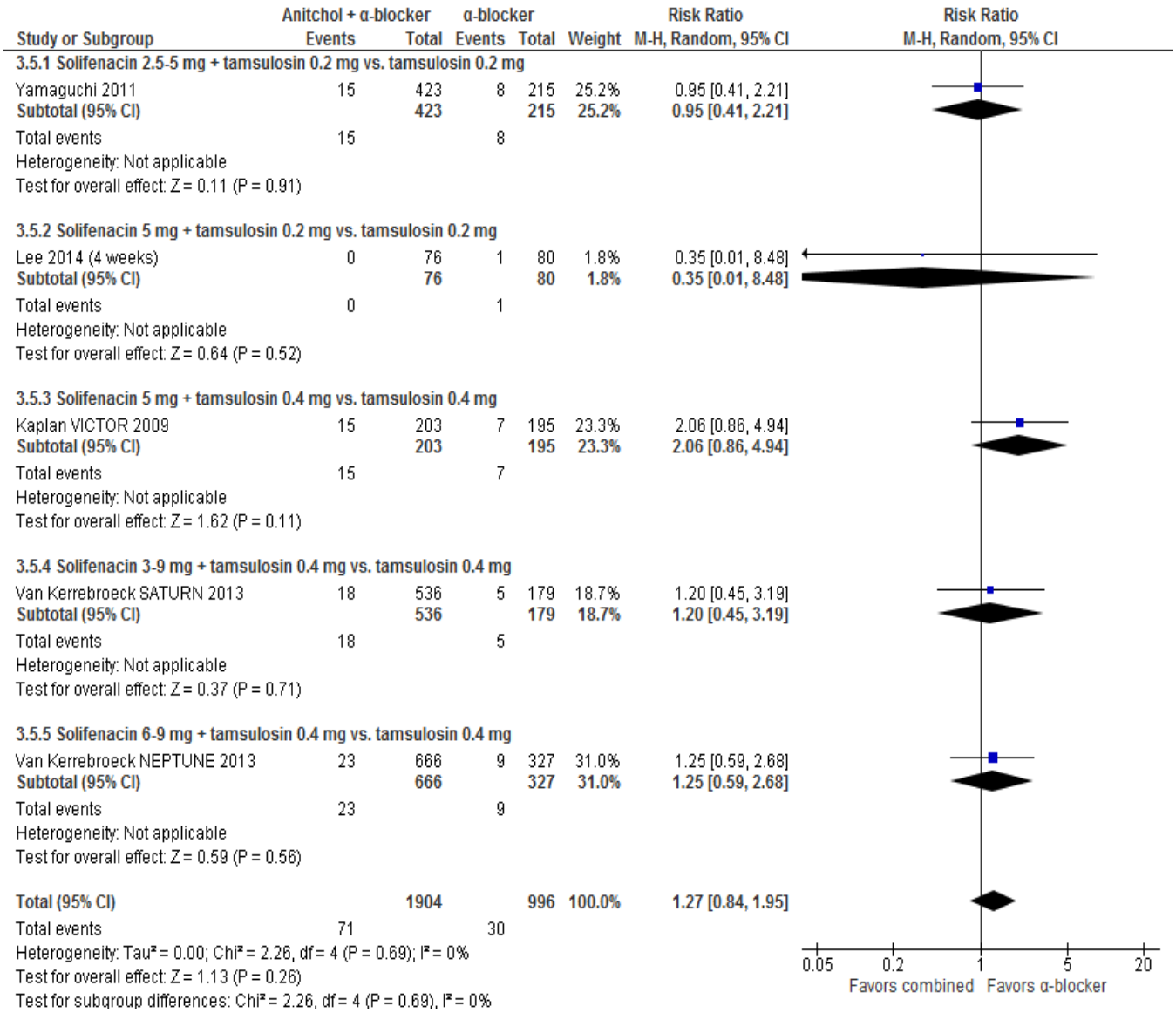


Figure E27. Patients with ≥1 adverse effect

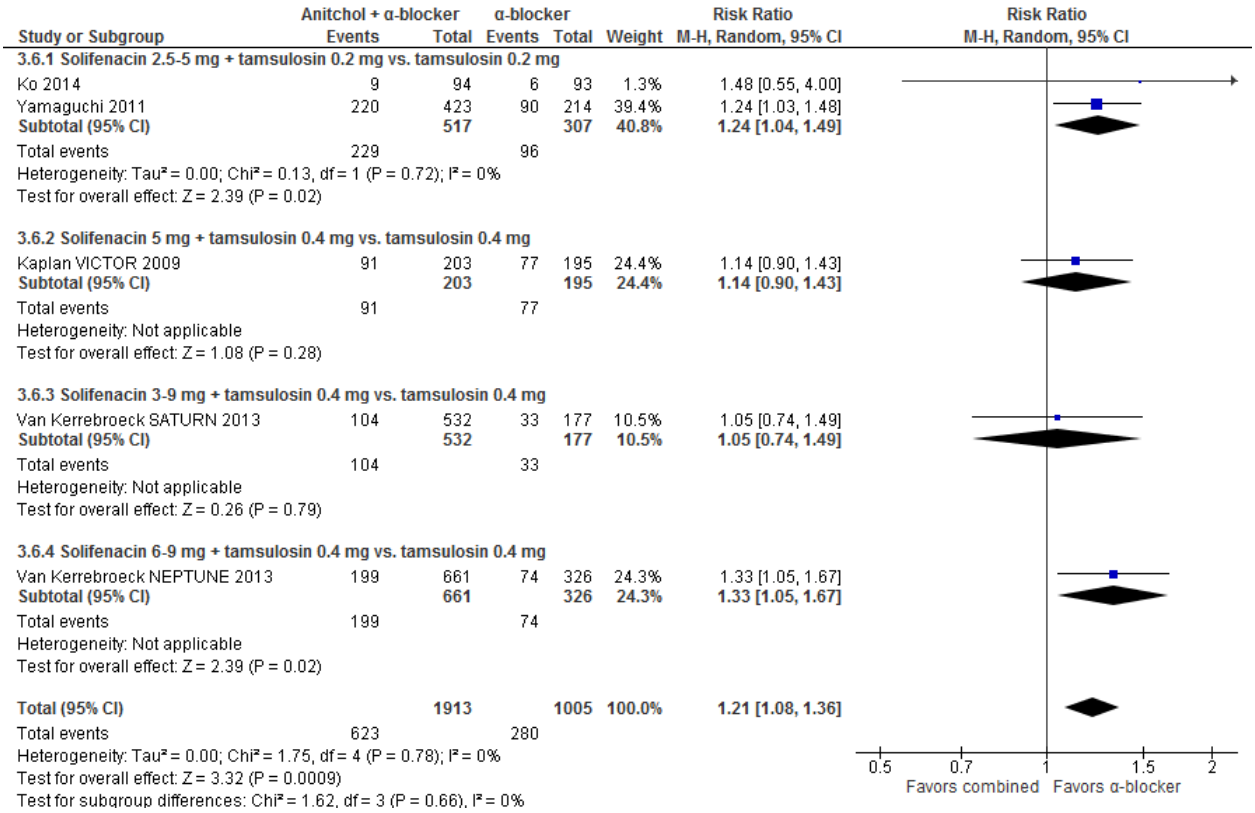


Figure E28. Dry mouth

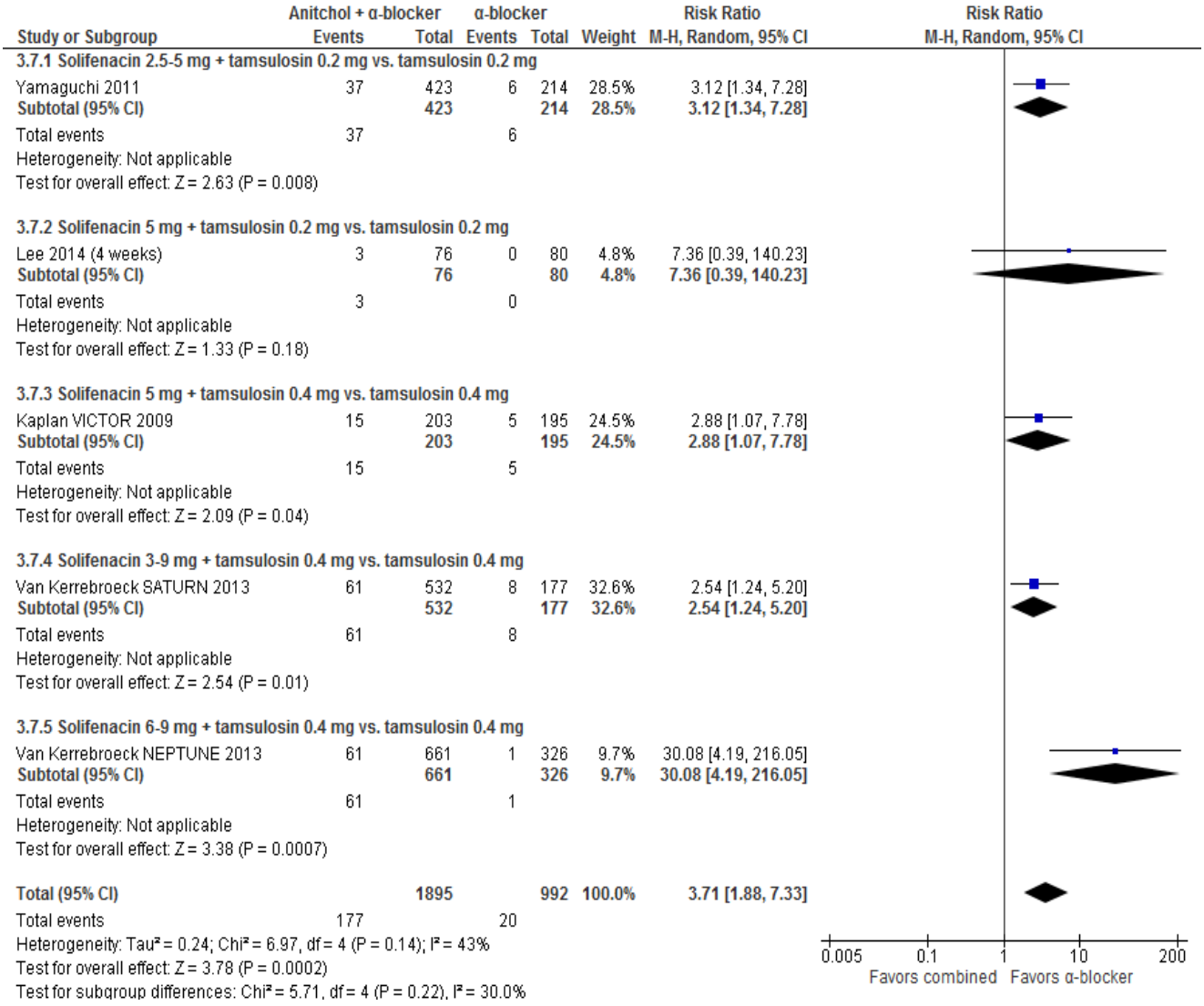


Figure E29. Constipation

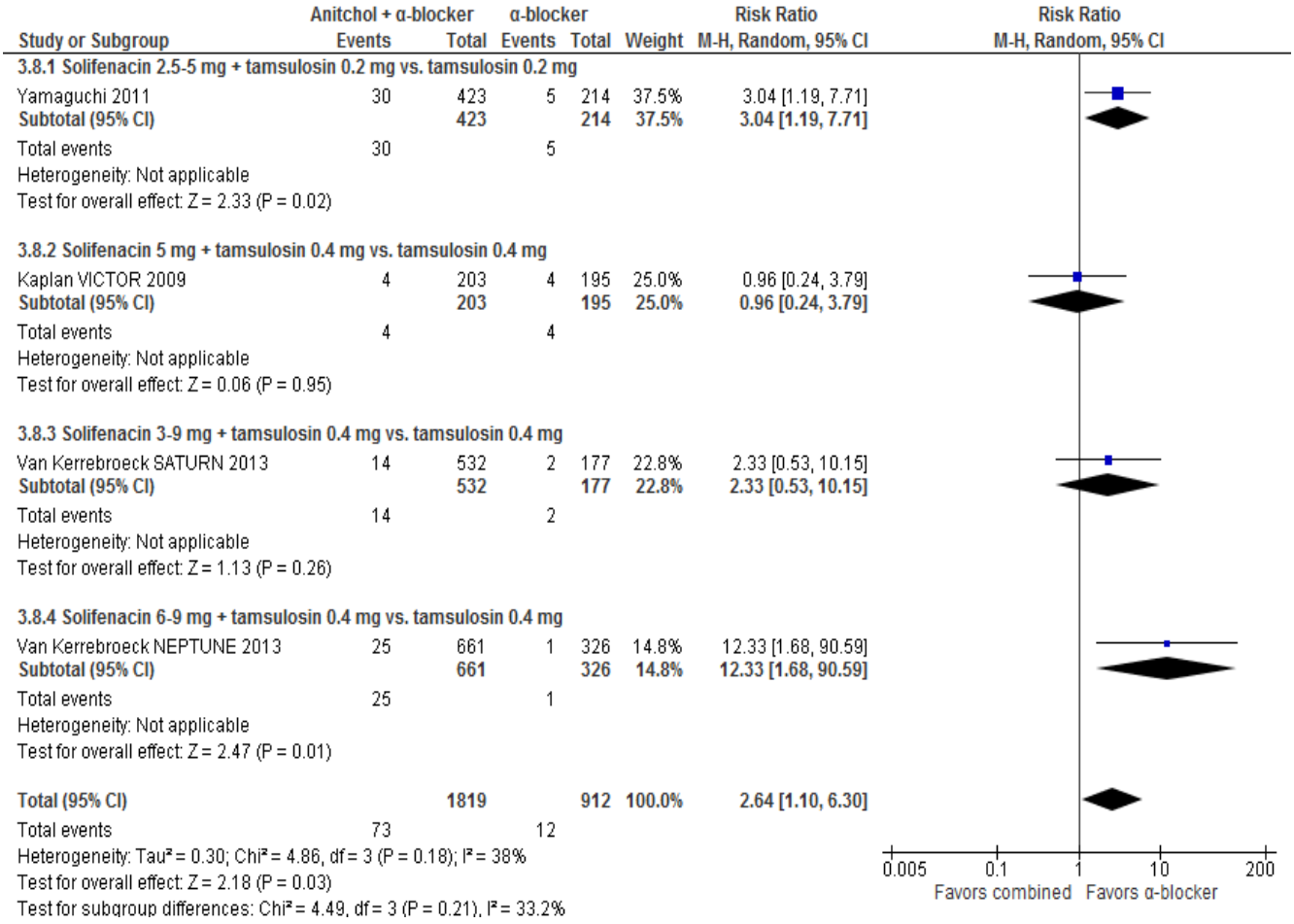


Table E5. Strength of evidence assessments: fesoterodine

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Fesoterodine, 4 to 8 mg plus unspecified alphablocker vs. unspecified AB	IPSS/AUA-SI , *mean change from baseline*	2 (990)	WMD=-0.07 [-0.88, 0.75]	Moderate	Direct	Precise	Consistent	Undetected	Low
	Overall withdrawals	1 (947)	RR=1.49 [1.06, 2.09]	Moderate	Direct	Precise	Consistent	Undetected	Low
	Withdrawals due to adverse effects	1 (947)	RR=2.30 [1.38, 3.82]	Moderate	Direct	Precise	Consistent	Undetected	Low
	Reporting >1 AE	1 (947)	RR=1.46 [1.25, 1.71]	Moderate	Direct	Precise	Consistent	Undetected	Low

[a] We searched and screened results from clinicaltrials.gov. We identified no eligible trials and detected no publication bias.

ARD=absolute risk difference; ARR=absolute risk reduction; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

Figure E30. Mean change in IPSS

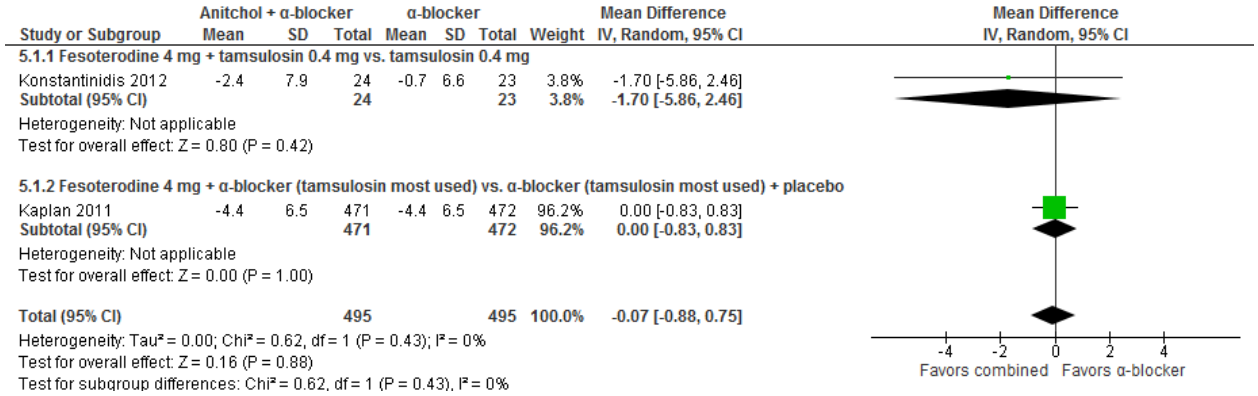


Figure E31. Withdrawals for any reason

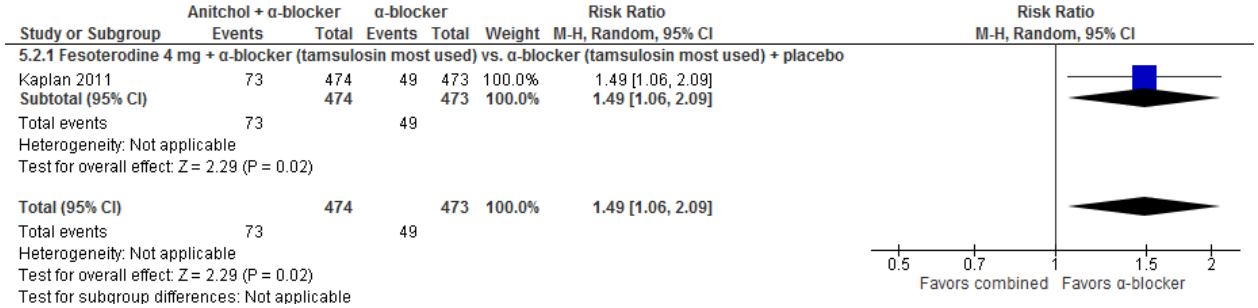


Figure E32. Withdrawals due to adverse effects

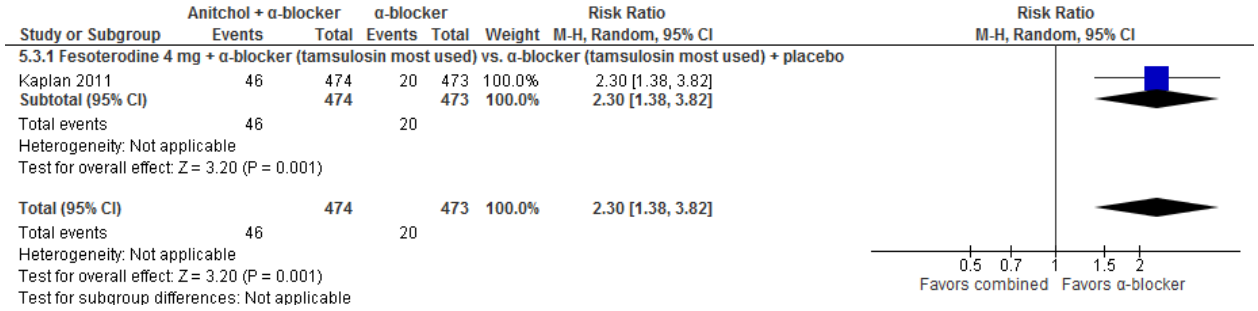


Figure E33. Proportion with ≥1 adverse effect

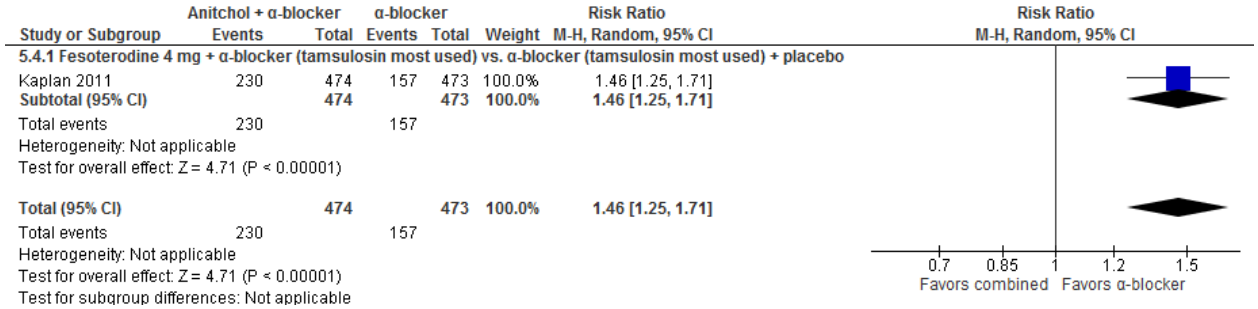


Table E6. Strength of evidence assessments: other anticholinergics

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Oxybutynin 10 mg plus tamsulosin 0.4 mg vs. tamsulosin 0.4 mg plus placebo	IPSS/AUA-SI , *mean change from baseline*	1 (420)	MD = -1.70 [-2.93 to -0.47]	Moderate	Direct	Precise	Unknown	Undetected	Low
	IPSS QoL, *mean change from baseline*	NR							Insufficient
	AUR	NR							Insufficient
	Overall withdrawals	NR							Insufficient
	Withdrawals due to adverse effects	NR							Insufficient
Trospium 45 mg plus terazosin 5 mg (alpha-blocker) vs. placebo plus terazosin 5 mg	IPSS/AUA-SI , *mean change from baseline*	1 (58)	Unable to determine MD	Moderate	Direct	Unclear	Unknown	Undetected	Insufficient
	IPSS QoL, *mean change from baseline*	NR							Insufficient
	AUR	NR							Insufficient
	Overall withdrawals	NR							Insufficient
	Withdrawals due to adverse effects	NR							Insufficient
	Participants with ≥1 adverse effect	1 (58)	RR = 1.47 [0.56 to 3.88	Moderate	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
Darifenacin 7.5 mg plus doxazosin 4 mg (alpha-blocker) vs. doxazosin 4 mg	IPSS/AUA-SI , *mean change from baseline*	1 (101)	MD = -3.47 [NR]	Moderate	Direct	Unknown	Unknown	Undetected[a]	Insufficient
	IPSS QoL, *mean change from baseline*	1 (101)	MD = -0.8 [NR]	Moderate	Direct	Unknown	Unknown	Undetected[a]	Insufficient
	Overall withdrawals	1 (101)	RR = 0.98 [0.020 to 48.50]	Moderate	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Withdrawals due to adverse effects	1 (101)	RR = 0.98 [0.020 to 48.50]	Moderate	Direct	Imprecise	Unknown	Undetected[a]	Insufficient

[a] We searched and screened results from clinicaltrials.gov. We identified no eligible trials and detected no publication bias.

ARD=absolute risk difference; ARR=absolute risk reduction; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

Appendix F. Supporting Tables: Mirabegron

Table F1. Risk of bias assessments: Mirabegron trials

Study	Overall Risk of Bias Assessment	Rationale
Ichihara, 2015[41]	High	Open label, outcome blinding not described, moderate attrition
Nitti, 2013[42]	Low	

Table F2. Characteristics of BPH treatment, comparison, and population: mirabegron trials

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Ichihara 2015[41] Japan N=94	T: Mirabegron 50 mg qd; tamsulosin 0.2 mg qd C: Tamsulosin 0.2mg qd	8 wk	I: Persistent OAB symptoms after tamsulosin 0.2 mg qd ≥8 wk; OABSS ≥3; urinary urgency ≥1 per wk E: PVR >100 mL; Qmax <5 mL/s; history of urinary retention neurogenic bladder, clean intermittent catheterization, severe bladder diverticulum, or urethral stricture; planning to have a child; suspected malignant disease; previous intrapelvic irradiation; suspected UTI; renal or hepatic impairment; taking medicine contraindicated to combination with mirabegron	Mean age: 75 Race: NR Baseline IPSS: 13.5
Nitti 2013[42] USA and Canada N=200	T_1: Mirabegron 100 mg qd T_2: Mirabegron 50 mg qd C: Placebo	12 wk	I: Age >45 yr; voiding/LUTS ≥3 mo; IPSS ≥8; BOOI ≥20; Qmax ≤12 mL/s; voided volume ≥120 mL during free flow E: History of urinary retention in prior 12 mo; history of carcinoma, prostate cancer, pelvic radiation therapy in prior 5 yr; neurogenic bladder; UTI or recurrent UTIs; previous or planned prostate surgery or other invasive procedures (excluding prostate biopsy) within 12 mo; chronic inflammation such as chronic prostatitis; stone in bladder or ureter; other causes of BOO such as bladder neck stenosis or urethral stricture	Mean age: 63 Race: 54% white Baseline IPSS: 19.9

BOO=bladder outlet obstruction; BOOI=bladder outlet obstruction index; BPH=benign prostatic hyperplasia; C=comparator group; E=exclusion criteria; I=inclusion criteria; IPSS=International Prostate Symptom Score; LUTS=lower urinary tract symptoms; mg=milligrams; mL=milliliters; NR=not reported; OAB=overactive bladder; OABSS=overactive bladder symptoms score; PVR= postvoid residual urine; qd=daily; Qmax=maximum urinary flow rate; s=second; T=treatment group; T_1=treatment group 1; T_2=treatment group 2; UTI=urinary tract infection; wk=weeks; yr=years

Table F3. Strength of evidence assessments: mirabegron

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Mirabegron 50 mg vs. placebo	IPSS score, *mean change from baseline*	1 (135)	MD= -5.7 [NR]	Low	Direct	Unknown	Unknown	Undetected[a]	**Insufficient**
	AUR	1 (135)	RR = 0 [0.01, 7.47]	Low	Direct	Imprecise	Unknown	Undetected[a]	**Insufficient**
	Overall withdrawals	1 (135)	RR = 1.39 [0.24, 8.07]	Low	Direct	Imprecise	Unknown	Undetected[a]	**Insufficient**
	Withdrawals due to adverse effects	1 (135)	RR = 0.93 [0.13, 6.40]	Low	Direct	Imprecise	Unknown	Undetected[a]	**Insufficient**
Mirabegron 100 mg vs. placebo	IPSS score, *mean change from baseline*	1 (130)	MD = -4.3 [NR]	Low	Direct	Unknown	Unknown	Undetected[a]	**Insufficient**
	AUR	1 (130)	RR = 1 [0.06, 15.65]	Low	Direct	Imprecise	Unknown	Undetected[a]	**Insufficient**
	Overall withdrawals	1 (130)	RR = 3.5 [0.76, 16.22]	Low	Direct	Imprecise	Unknown	Undetected[a]	**Insufficient**
	Withdrawals due to adverse effects	1 (130)	RR = 1 [0.15, 6.89]	Low	Direct	Imprecise	Unknown	Undetected[a]	**Insufficient**
Mirabegron 50 mg qd plus alpha-blocker vs. alpha-blocker	IPSS/AUA-SI , *mean change from baseline*	1 (94)	MD = 2.08 [NR]	High	Direct	Unknown	Unknown	Undetected[a]	**Insufficient**
	IPSS QoL, *mean change from baseline*	1 (94)	MD= -0.71 [NR]	High	Direct	Unknown	Unknown	Undetected[a]	**Insufficient**
	AUR	1 (94)	RR = 2.66 [0.11, 63.40]	High	Direct	Imprecise	Unknown	Undetected[a]	**Insufficient**
	Overall withdrawals	1 (94)	RRR = 9.75 [0.56, 170.43]	High	Direct	Imprecise	Unknown	Undetected[a]	**Insufficient**
	Withdrawals due to adverse effects	1 (94)	RR = 9.75 [0.56, 170.73]	High	Direct	Imprecise	Unknown	Undetected[a]	**Insufficient**

[a] We searched and screened results from clinicaltrials.gov. We identified one eligible trial that has not yet been completed. We detected no publication bias.
ARD=absolute risk difference; ARR=absolute risk reduction; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference
* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

Appendix G. Supporting Tables and Figures: PDE-5s

Table G1. Risk of bias assessments: PDE-5 trials

Study	Overall Risk of Bias Assessment	Rationale
Casabe, 2014[43]	Low	
Kumar, 2014[44]	High	Randomization methods not reported, different pills taken at different times, inadequate patient and provider blinding; assessors likely unblinded, no attrition
Singh, 2014[45]	High	Allocation methods unclear, open label
Takeda, 2014[46]	Low	Randomization and allocation methods unclear.
Abolyosr, 2013[47]	High	Randomization and allocation methods unclear, unblinded and no placebo, no between group analyses, attrition unclear
Regadas, 2013[48]	Moderate	Allocation methods unclear, small sample size, attrition unclear
Yokoyama, 2013[49]	Moderate	Allocation methods unclear, baseline reported with standard deviation but results reported with standard error
Egerdie, 2012[50]	Low	
Gacci, 2012[51]	Moderate	
Goldfischer, 2012[52]	Low	
Madani, 2012[53]	Moderate	Allocation methods unclear, “standard therapy” differed between treatment groups, no between group analyses, no attrition
Oelke, 2012[54]	Low	
Ozturk, 2012[55]	High	Allocation methods unclear, unblinded and no placebo, moderate sample size, some results not reported
Takeda, 2012[56]	Low	
Kim, 2011[57]	Moderate	Allocation methods unclear. groups similar at baseline except for history of erectile dysfunction, pilot study, baseline reported with standard deviation but results reported with standard error
Porst, 2011[58]	Low	
Dmochowski, 2010[59]	Moderate	Completer analysis
Tuncel, 2010[60]	Moderate	Randomization methods not reported, unblinded and no placebo, small sample size, some key outcomes reported in figures only
Liguori, 2009[61]	High	Allocation methods unclear, open label, no between group analyses, completer analysis
Roehrborn, 2008[62]	Low	
Stief, 2008[63]	Low	
McVary, 2007a[64]	Low	
McVary, 2007b[65]	Moderate	Allocation methods unclear, one-sided alpha level used, unclear how attrition handled
Kaplan, 2007[66]	High	Randomization and allocation methods unclear, unblinded and no placebo, small sample size

Table G2. Characteristics of BPH treatment, comparison, and population: PDE-5 trials

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Casabe, 2014[43] North America, South America, Europe N=696	T: Tadalafil 5 mg qd; finasteride 5 mg qd C: Finasteride qd	12 wk	I: Age >45 yr; IPSS ≥13; LUTS/BPH >6 mo; prostate volume ≥30 mL; Qmax 5-15 mL/s; naïve to 5-ARIs E: NR	Mean age: 64 Race: 86% white Baseline IPSS: 17.3
Kumar, 2014[44] India N=75	T_1: Tadalafil 10 mg qd; afluzosin 10 mg qd T_2: Tadalafil 10 mg qd C_1: Afluzosin 10 mg qd	12 wk	I: Age >50 yr; IPSS ≥8 E: According to the specified contraindications of both the drugs	Mean age: 62 Race: NR Baseline IPSS: 17.8
Singh, 2014[45] India N=133	T_1: Tadalafil 10 mg qd; tamsulosin 0.4 mg qd T_2: Tadalafil 10 mg qd C: Tamsulosin 0.4 mg qd	13 wk	I: Age >45 yr; IPSS ≥8; LUTS/BPH ≥6 mo; PSA ≤4.0 ng/mL; Qmax 5-15 mL/s; voided volume >125 mL E: Contraindications to drugs in study; use of finasteride/dutasteride or prohibited medications like alpha agonists; syncope, orthostatic hypotension; BOO due to cancer, calculi or stricture; previous TURP; any neurological disorders affecting storage and voiding; prostatitis or cancer; recent AUR; UTI; poorly controlled diabetes mellitus or hypertension	Mean age: 61 Race: NR Baseline IPSS: 21.0
Takeda, 2014[46] Lee, 2014[67] Japan, Korea N=610	T: Tadalafil 5 mg qd C: Placebo	12 wk	I: Age ≥45 yr; IPSS ≥13; Qmax 4-15 mL/s; prostate volume >20 mL; PVR <300 mL E: PSA >10 ng/mL (or ≥4 ng/mL if prostate cancer could not be ruled out); sugary on pelvic urinary tract; recent finasteride, dutasteride, anti-androgenic hormone therapy, or other BPH, ED or OAB therapies	Mean age: 61 Race: NR Baseline IPSS: 18.7
Abolyosr, 2013[47] Egypt N=150	T_1: Sildenafil 50 mg; doxazosin 2 mg T_2: Sildenafil 50 mg C: Doxazosin 2 mg	17 wk	I: Age ≥45 yr; IPSS >7; LUTS/ BPH ≥3; ED ≥3 mo; IIEF-EF <25 E: Previous prostatic surgery or other surgery for BPH; cystitis or bladder stones; PSA >10; contraindications for medical treatment for ED (cardiac problems which contraindicate the use of PDE-5 inhibitors, needing surgery); previous unresponsiveness to PDE‑5s	Mean age: NR Race: NR Baseline IPSS: 16.7
Regadas, 2013[48] Brazil N= 40	T: Tadalafi 5 mg qd; tamsulosin 0.4 mg qd C: Placebo; tamsulosin 0.4 mg qd	4 wk	I: Age ≥45 yr; IPSS >14; LUTS secondary to BPH; BOOI >20 E: Prostate cancer, LUTS not related to BPH, hypotension, retinitis pigmentosa; recent 5-ARIs, ABs, anticholinergics, PDE-5s; surgery of the prostate, urethra, or bladder; neurological disease, urinary retention, bladder stones; use of nitrates; cardiovascular, hepatic, or renal insufficiency	Mean age: 61 Race: NR Baseline IPSS: 20.5

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Yokoyama, 2013[49] Lee 2014[67] Japan, Korea, Taiwan N=1224	T_1: Tadalafil 2.5 mg qd T_2: Tadalafil 5 mg qd C_1: Placebo C_2: Tamsulosin 0.2 mg qd	12 wk	I: Age ≥45 yr; IPSS ≥13; Qmax 4 - 15 mL/s; prostate volume ≥20 mL; LUTS >6 mo; PVR <300 mL E: PSA >10 ng/mL (or PSA 4 - 10 ng/mL, unless clinically negative for prostate cancer); history of symptomatic orthostatic hypotension, dizziness, vertigo, LOC, or syncope; clinical prostate cancer or urinary tract conditions affecting LUTS; severe renal or hepatic insufficiency; recent finasteride or dutasteride; cardiac conditions or nitrate use	Mean age: 63 Race: NR Baseline IPSS: 16.8
Egerdie, 2012[50] Roehrborn, 2014[68] Porst, 2013[69] Porst, 2013[70] Brock, 2014[71] Oelke, 2014[72] Europe, Mexico, USA N=806	T_1: Tadalafil 2.5 mg qd T_2: Tadalafil 5 mg qd C: Placebo	12 wk	I: Age ≥45 yr; IPSS ≥13; LUTS >6 mo and ED ≥3 mo; Qmax 4-15 mL/s; ≥4 intercourse attempts; 70% compliant during run-in; PVR <300 mL E: PSA >10 ng/mL (or PSA 4-10 ng/mL, unless cancer ruled out); ED due to other primary sexual disorders or endocrine disease; prior nonresponsiveness to PDE5s; certain cardiac conditions; recent finasteride or dutasteride; recent lower urinary tract instrumentation; urethral or intravesicle obstruction; recent urinary retention or stones; neurogenic bladder, renal insufficiency, or hepatic impairment	Mean age: 63 Race: 93% white Baseline IPSS: 18.3
Gacci, 2012[51] Italy N=60	T: Vardenafil 10 mg qd; tamsulosin 0.4 mg qd C: Placebo; tamsulosin 0.4 mg qd	12 wk	I: Age 40–80 yr; LUTS (IPSS ≥12, OAB questionnaire-Short Form ≥8); voided volume <400 mL; Qmax >5 mL/s (with a voided volume >150 mL) E: Hypersensitivity to vardenafil or tamsulosin; drugs incompatible with vardenafil or tamsulosin; bladder failure (abnormal urodynamic assessment in men with PVR >250 mL); neurogenic bladder (multiple sclerosis, Parkinson, spinal cord injury), UTI, LUT disease/treatment (urethral stenosis, 5-ARI, or BPH surgery); severe systemic disease (hepatic, cardiac, hematological, or neoplastic); unable to complete the protocol	Mean age: 68 Race: 100% white Baseline IPSS: 19.6
Goldfischer, 2012[52] USA N= 318	T: Tadalafil 5 mg qd; AB C: Placebo; AB	12 wk	I: Age ≥45 yr; LUTS from BPH >6 mo; stable dose of AB for BPH ≥4 wk E: PSA >10 ng/mL (or PSA ≥4 to <10 ng/mL, unless malignancy ruled out; PVR ≥300 mL; AB for hypertension	Mean age: 67 Race: 89% white Baseline IPSS: 13.6
Madani, 2012[53] Iran N=132	T: Tadalafil 10 mg qd; standard treatment (AB or finasteride) C: Placebo; standard treatment (AB or finasteride)	13 wk	I: IPSS ≥8; LUTS/BPH; Qmax 5-15 mL/s; no indication for surgical intervention; had reached plateau levels of response to standard treatment E: History of refractory urinary retention, persistent gross hematuria, recurrent UTI renal insufficiency, bilateral hydronephrosis or bladder stones due to BPH; spinal cord injury, prostatitis, bladder or prostate malignancy, bladder neck or urethral stricture, PVR >120; pelvic trauma	Mean age: 65 Race: NR Baseline IPSS: 13.4

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
			or surgery; recent myocardial infarction, unstable angina; use of nitrates or nitric oxide donors, androgens or anti-androgens, anticoagulants, cytochrome p-450 3A4 inhibitors	
Oelke, 2012[54] Oelke, 2014[73] Roehrborn, 2014[68] Porst, 2013[69] Porst, 2013[70] Brock, 2013[74] Brock, 2014[71] Oelke, 2014[72] Europe, Mexico, Australia N=682	T: Tadalafil 5 mg qd C_1: Placebo C_2: Tamsulosin 0.4 mg qd	12 wk	I: Age ≥45 yr; IPSS ≥13; history of LUTS secondary to BPH for >6 mo; Qmax 4 - 15 mL/s; compliance during run-in ≥70% E: PSA >10 ng/mL (PSA 4-10 ng/mL, unless negative biopsy); recentfinasteride or dutasteride, recent lower urinary tract instrumentation or stones, or urinary retention; history of urethral or bladder neck obstruction; neurogenic bladder; creatinine clearance <30 mL/min; severe hepatic impairment; certain cardiovascular conditions; current nitrate therapy; planned cataract surgery; symptomatic orthostatic hypotension, recurrent dizziness, vertigo, loss of consciousness, syncope	Mean age: 64 Race: 77% white Baseline IPSS: 17.1
Ozturk, 2012[55] Turkey N=100	T: Sildenafil 50 mg; alfuzosin XL 10 mg C: Alfuzosin XL 10 mg	13 wk	I: Age >45 yr; IPSS ≥12, QoL ≥3; moderate-to-severe LUTS; naïve to treatment for LUTS or ED E: Contraindications to alfuzosin or sildenafil; bladder stones or previous prostatic operations; history of AUR; urethral strictures, PVR >200 mL; prostate cancer, chronic renal or liver insufficiency	Mean age: NR Race: NR Baseline IPSS: 19.9
Takeda, 2012[56] Japan N=562	T_1: Tadalafil 2.5 mg qd T_2: Tadalafil 5 mg qd C: Placebo	12 wk	I: Age ≥45 yr; IPSS ≥13; Qmax 4 - 15 mL/s; prostate volume >20 mL; PVR <300 mL E: PSA >10 ng/mL (or PSA 4-10 ng/mL, unless clinically negative for prostate cancer); sugary on pelvic urinary tract; clinical prostate cancer or urinary tract conditions affecting LUTS; renal insufficiency; recent dutasteride	Mean age: 67 Race: NR Baseline IPSS: 16.4
Kim, 2011[57] Lee, 2014[67] Korea N= 202	T: Tadalafil 5 mg qd C_1: Tamsulosin 0.2 mg qd C_2: Placebo	12 wk	I: Age ≥45 yr; IPSS ≥13; Qmax 4-15 mL/s; LUTS >6 mo; PVR ≤300 mL E: PSA >10 ng/mL (PSA 4-10 ng/mL, unless negative biopsy); history of symptomatic orthostatic hypotension, dizziness, vertigo, LOC, or syncope; recent finasteride or dutasteride; other BPH, ED or OAB therapies	Mean age: 62 Race: NR Baseline IPSS: 17.4
Porst, 2011[58] Roehrborn, 2014[68] Porst, 2013[69] Porst, 2013[70] Brock, 2013[74]	T: Tadalafil 5 mg qd C: Placebo	12 wk	I: Age ≥45 yr; IPSS ≥13; history of LUTS secondary to BPH for >6 mo; Qmax 4 - 15 mL/s; PVR ≤300 mL; compliance during run-in ≥70% E: PSA >10 ng/mL (PSA 4-10 ng/mL, unless negative biopsy); recent finasteride or dutasteride, recent lower urinary tract instrumentation or stones, or urinary retention; history of urethral or bladder neck	Mean age: 65 Race: 92% white Baseline IPSS: 16.8

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
Brock, 2014[71] Oelke, 2014[72] Argentina, Germany, Italy, Mexico, US N=325			obstruction; neurogenic bladder; creatinine clearance <30 mL/min; severe hepatic impairment; certain cardiovascular conditions; current nitrate therapy	
Dmochowski, 2010[59] Dmochowski, 2013[76] USA, Canada N=200	T: Tadalafil 20 mg qd C: Placebo	12 wk	I: Age ≥40 yr; IPSS ≥13; LUTS >6 mo; PVR <350 mL E: PSA >10 ng/mL (PSA 4-10 ng/mL, unless negative biopsy); recent 5-ARIs; penile or pelvic surgery, radiotherapy, malignancy, trauma, instrumentation; urinary retention or stones; urethral obstruction; atonic, decompensated or hypocontractile bladder; detrusor-sphincter dyssynergia; intravesical obstruction; urinary tract inflammation or infection	Mean age: 59 Race: 77% white Baseline IPSS: 21.7
Tuncel, 2010[60] Turkey N= 60	T_1: Sildenafil 25 mg qd 4d/wk; tamsulosin 0.4 mg qd T_2: Sildenafil 25 mg qd 4 d/wk C: Tamsulosin 0.4 mg qd	8 wk	I: IPSS ≥12; SHIM ≤20; BPH/LUTS and ED E: Drugs or surgery for BPH or ED, recent prostate biopsy or 5-ARIs; any urologic cancer, prostate or bladder/pelvic radiation or surgery, urinary stone, active UTI, recent AUR; recent urethral catheter; acute or chronic hepatic failure, renal dysfunction; poorly controlled diabetes, nitrates use	Mean age: NR Race: NR Baseline IPSS: 15.3
Liguori, 2009[61] Italy N=66	T_1: Tadalafil 20 mg every other day; alfuzosin extended release 10 mg qd T_2: Tadalafil 20 mg qd C: Alfuzosin extended release 10 mg qd	12 wk	I: Age 50–75 yr; IPSS >8; LUTS/BPH ≥6 mo; untreated ED of any grade E: Contraindications of either drug; medications to control bladder symptoms; bladder tumors, urethral strictures, neurogenic bladder dysfunction, prostatitis, prostate cancer, PSA >20 ng/mL; prostate surgery or radiotherapy, AUR or indwelling catheter; acute UTI; ever used 5-ARIs, ABs, or PDE-5s	Mean age: 62 Race: NR Baseline IPSS: 14.9
Roehrborn, 2008[62] Broderick, 2010[77] Roehrborn, 2014[68] Porst, 2013[69] Porst, 2013[70] Brock, 2013[74] Brock, 2014[71] Oelke, 2014[72] 10 countries N=1689	T_1: Tadalafil 2.5 mg qd T_2: Tadalafil 5 mg qd T_3: Tadalafil 20 mg qd C: Placebo	12 wk	I: Age ≥45 yr; IPSS ≥13; history of LUTS secondary to BPH for ≥6 mo; Qmax 4 - 15 mL/s; PVR ≤300 mL E: PSA >10 ng/mL (PSA 4 - 10 ng/mL, unless negative biopsy); recent finasteride or dutasteride, antiandrogens, or potent cytochrome P450 3A4 inhibitor; penile or pelvic problems other than LUTS/BPH; clinically significant renal, hepatic, cardiovascular, or diabetic disease; spinal cord injury, cancer chemotherapy	Mean age: 62 Race: 85% white Baseline IPSS: 17.3
Stief,2008[63] Germany	T: Vardenafil 10 mg bid C: Placebo	8 wk	I: Age 45–64 yr; IPSS ≥12; LUTS ≥6 mo	Mean age: 56 Race: 99% white

Study Country Number Randomized	Intervention Comparisons	Duration	Inclusion/Exclusion Criteria	Population Characteristics
N=222			E: Contraindications to vardenafil; spinal cord injury; prostatitis; history of prostate or bladder cancer; bladder or urethra stricture; PVR ≥100 mL; pelvic trauma or surgery; any malignancies; life expectancy of <3 yr; use of nitrates or nitric oxide donors, androgens or anti-androgens, anticoagulants, cytochrome P-450 3A4 inhibitors, alpha1-blockers, or any treatment for ED	Baseline IPSS: 16.8
McVary, 2007a[64] McVary, 2008[78] USA N=370	T: Sildenafil 50-100 mg C: Placebo	12 wk	I: Age ≥45 yr; IPSS ≥12; IIEF-EF ≤25 E: PSA >10 ng/mL (or PSA 4-10 ng/mL, unless clinically negative for prostate cancer), prostate cancer, prostate/bladder/pelvic radiation or surgery; causes of symptoms other than BPH (urinary tract disease, recent cystoscopy, urinary calculi, AUR, recurrent UTIs, recent catheterization for outflow obstruction); hypotension, hypertension, orthostatic hypotension, or significant cardiovascular disease; hepatic or renal disease, poorly-controlled diabetes, retinitis pigmentosa; use of nitrates, antimuscarinics, recent 5-ARIs, recent ABs	Mean age: 60 Race: 82% white Baseline IPSS: NR
McVary, 2007b[65] USA N= 543	T_1: Tadalafil 5 mg T_2: Tadalafil 20 mg C: Placebo	6 wk	I: Age ≥45 yr; LUTS/BPH ≥6 mo; agreed not to use other BPH meds E: PSA >10 ng/mL (PSA 4 - 10 ng/mL, unless negative biopsy); recent finasteride or dutasteride; radical prostatectomy or other pelvic surgery; neurological condition affecting bladder function; recent lower urinary tract instrumentation, retention or stones; past urethral obstruction; detrusor-sphincter dyssynergia; UTI or urinary tract inflammation; intravesical obstruction due to the prostate median lobe; prostate cancer; PVR ≥ 200 mL at visit 2; certain cardiovascular diseases, clinically significant renal or hepatic insufficiency, recent stroke or spinal cord injury; current nitrates, cancer chemotherapy, antiandrogens or a potent cytochrome P450 3A4 inhibitor; or HbA1c >9%	Mean age: 62 Race: 81% white Baseline IPSS: 17.9
Kaplan, 2007[66] USA N= 124	T_1: Sildenafil 25 mg qd; alfuzosin 10 mg qd T_2: Sildenafil 25 mg qd C: Alfuzosin 10 mg qd	12 wk	I: Age 50-76 yr; moderate to severe untreated LUTS and self-reported ED E: NR	Mean age: 64 Race: NR Baseline IPSS: 17.3

AB=alpha blocker; ARI=alpha-reductase inhibitor; AUR=acute urinary retention; bid=twice daily; BOO=bladder outlet obstruction; BOOI=bladder outlet obstruction index; BPH=benign prostatic hyperplasia; d=days; C=comparator group; C_1=comparator group 1; C_2=comparator group 2; dL=deciliters; E=exclusion criteria; ED=erectile dysfunction; HbA1c= glycated haemoglobin; HRQL=health-related quality of life; I=inclusion criteria; IIEF-EF=international index of erectile function questionnaire-erectile function subscale; IPSS=International Prostate Symptom Score; LOC=loss of consciousness; LUTS=lower urinary tract symptoms; mg=milligrams; min=minute; mL=milliliters; ng=nanograms; NR=not reported; OAB=overactive bladder; PDE-5=phosphodiesterase-5 inhibitors; prn=as needed; PSA=prostate-specific antigen; PVR= postvoid residual urine; qd=daily; Qmax=maximum urinary flow rate; QoL=quality of life; s=seconds; SHIM=sexual health inventory for men; T=treatment group; T_1=treatment group 1; T_2=treatment group 2; TURP=transurethral resection of the prostate; UTI=urinary tract infection; wk=weeks; yr=years

Table G3. Strength of evidence assessments: tadalafil

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Tadalafil 5 mg vs. placebo	IPSS/AUA-SI , *mean change from baseline*	9 (3024)	WMD -1.79 (-2.21, -1.37)	Low	Direct	Imprecise	Consistent	Undetected[a]	Moderate
	Responders – change from baseline of ≥3 points in IPSS scores	1 (281)	RR 1.36 (1.03 to 1.78)	Low	Direct	Precise	Unknown	Undetected[a]	Low
	BII, *mean change from baseline*	7 (2161)	WMD -0.52 (-0.74 to -0.30)	Low	Direct	Imprecise	Consistent	Undetected[a]	Moderate
	IPSS QoL, *mean change from baseline*	8 (2605)	WMD -0.27 (-0.38 to -0.17) SMD -0.20 (-0.27 to -0.12]	Low	Direct	Precise	Consistent	Undetected[a]	Moderate
	Overall withdrawals	9 (3082)	RR 1.00 (0.80 to 1.26)	Low	Direct	Imprecise	Consistent	Undetected[a]	Moderate
	Withdrawals due to adverse effects	9 (3082)	RR 1.80 (1.07 to 3.04)	Low	Direct	Precise	Consistent	Undetected[a]	High
	Participants with ≥1 adverse effect	9 (3082)	RR 1.25 (1.10 to 1.42)	Low	Direct	Precise	Consistent	Undetected[a]	High
Combined tadalafil 5-20 mg with any alpha-blocker vs. any alpha-blocker	IPSS/AUA-SI , *mean change from baseline*	4 (214)	WMD -2.02 (-3.26, -0.77)	High	Direct	Imprecise	Consistent	Undetected[a]	Low
	IPSS QoL, *mean change from baseline*	3 (174)	WMD -0.44 (-0.61, -0.26) SMD -0.71 (-1.02 to -0.41)	High	Direct	Precise	Consistent	Undetected[a]	Low
	Overall withdrawals	4 (224)	RR 0.80 (0.25 to 2.50)	High	Direct	Imprecise	Consistent	Undetected[a]	Insufficient
	Withdrawals due to adverse effects	4 (224)	RR 1.13 (0.29 to 4.33)	High	Direct	Imprecise	Consistent	Undetected[a]	Insufficient
	Participants with ≥1 adverse effect	NR							Insufficient
Tadalafil 5 mg vs. tamsulosin 0.2-0.4 mg	IPSS/AUA-SI , *mean change from baseline*	3 (742)	WMD 0.07 (-0.88 to 1.02)	Moderate	Direct	Precise	Consistent	Undetected[a]	Moderate
	BII, *mean change from baseline*	3 (731)	WMD -0.02 (-0.70 to 0.66)	Moderate	Direct	Imprecise	Inconsistent	Undetected[a]	Insufficient

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
	IPSS QoL, *mean change from baseline*	3 (742)	WMD -0.01 (-0.38 to 0.37)	Moderate	Direct	Precise	Inconsistent	Undetected[a]	Low
	Overall withdrawals	3 (742)	RR 1.35 (0.64 to 2.85)	Moderate	Direct	Imprecise	Consistent	Undetected[a]	Low
	Withdrawals due to adverse effects	3 (742)	RR 2.68 (0.85 to 8.39)	Moderate	Direct	Imprecise	Consistent	Undetected[a]	Insufficient
	Participants with ≥1 adverse effect	3 (742)	RR 0.99 (0.67 to 1.46)	Moderate	Direct	Imprecise	Consistent	Undetected[a]	Low
Tadalafil 10-20 mg vs. alfuzosin 10 mg	IPSS/AUA-SI, *mean change from baseline*	2 (87)	WMD 3.33 (1.98 to 4.68)	High	Direct	Imprecise	Consistent	Undetected[a]	Low
	IPSS QoL, *mean change from baseline*	2 (87)	WMD 0.61 (0.13 to 1.08) SMD 0.65 (-0.02 to 1.32)	High	Direct	Imprecise	Consistent	Undetected[a]	Low
	Overall withdrawals	2 (93)	RR 0.52 (0.11 to 2.56)	High	Direct	Imprecise	Consistent	Undetected[a]	Insufficient
	Withdrawals due to adverse effects	2 (93)	RR 0.35 (0.04 to 3.10)	High	Direct	Imprecise	Consistent	Undetected[a]	Insufficient
	Participants with ≥1 adverse effect	NR							Insufficient
Tadalafil 5 mg & finasteride 5 mg vs. Placebo & finasteride 5 mg	IPSS/AUA-SI, mean change from baseline	1 (696)	MD -1.0 (-1.9 to -0.2)	Low	Direct	Precise	Unknown	Undetected	Low
	IPSS QoL, *mean change from baseline*	1 (696)	MD -0.2 (-0.4 to 0.0)	Low	Direct	Precise	Unknown	Undetected	Low
	Overall withdrawals	1 (696)	RR = 0.63 [0.44, 0.91]	Low	Direct	Precise	Unknown	Undetected	Low
	Withdrawals due to adverse effects	1 (696)	RR = 1.50 [0.44, 5.06]	Low	Direct	Imprecise	Unknown	Undetected	Insufficient
	Participants with ≥1 adverse effect	1 (696)	RR = 1.15 [0.91, 1.45]	Low	Direct	Imprecise	Unknown	Undetected	Insufficient
Tadalafil 10 mg & AB OR finasteride vs. Placebo & AB OR finasteride	IPSS/AUA-SI, mean change from baseline	1 (132)	MD -3.1 (-4.5 to -1.7)	Moderate	Direct	Imprecise	Unknown	Undetected	Insufficient
	IPSS QoL, *mean change from baseline*	1 (132)	MD -0.6 (-0.9 to -0.3)	Moderate	Direct	Imprecise	Unknown	Undetected	Insufficient

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Study Limitations	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
	Withdrawals due to adverse effects	1 (132)	RR = 1.50 [0.44, 5.07]	Moderate	Direct	Imprecise	Unknown	Undetected	Insufficient

[a] We searched and screened results from clinicaltrials.gov. We identified 14 eligible trials; 12 had been published and included in our review. The two that are not yet published have only recently completed. We detected no publication bias.

ARR=absolute risk reduction; ARD=absolute risk difference; BII = BPH Impact Index; NA=not applicable; NR=not reported; RR=risk ratio

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

Efficacy of Tadalafil

Figure G1. IPSS responders (≥3 points from baseline): tadalafil vs. placebo

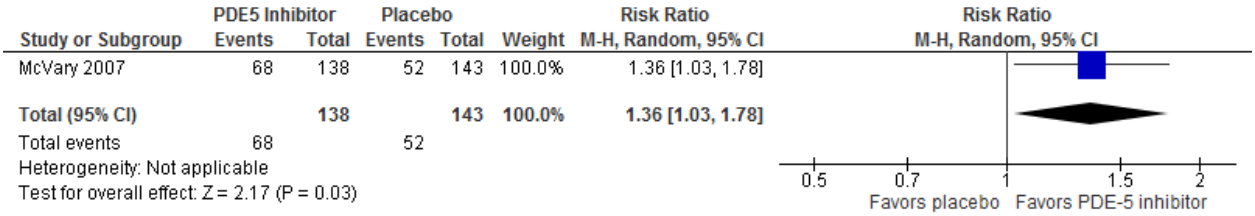


Figure G2. IPSS scores, mean change from baseline: tadalafil vs. placebo

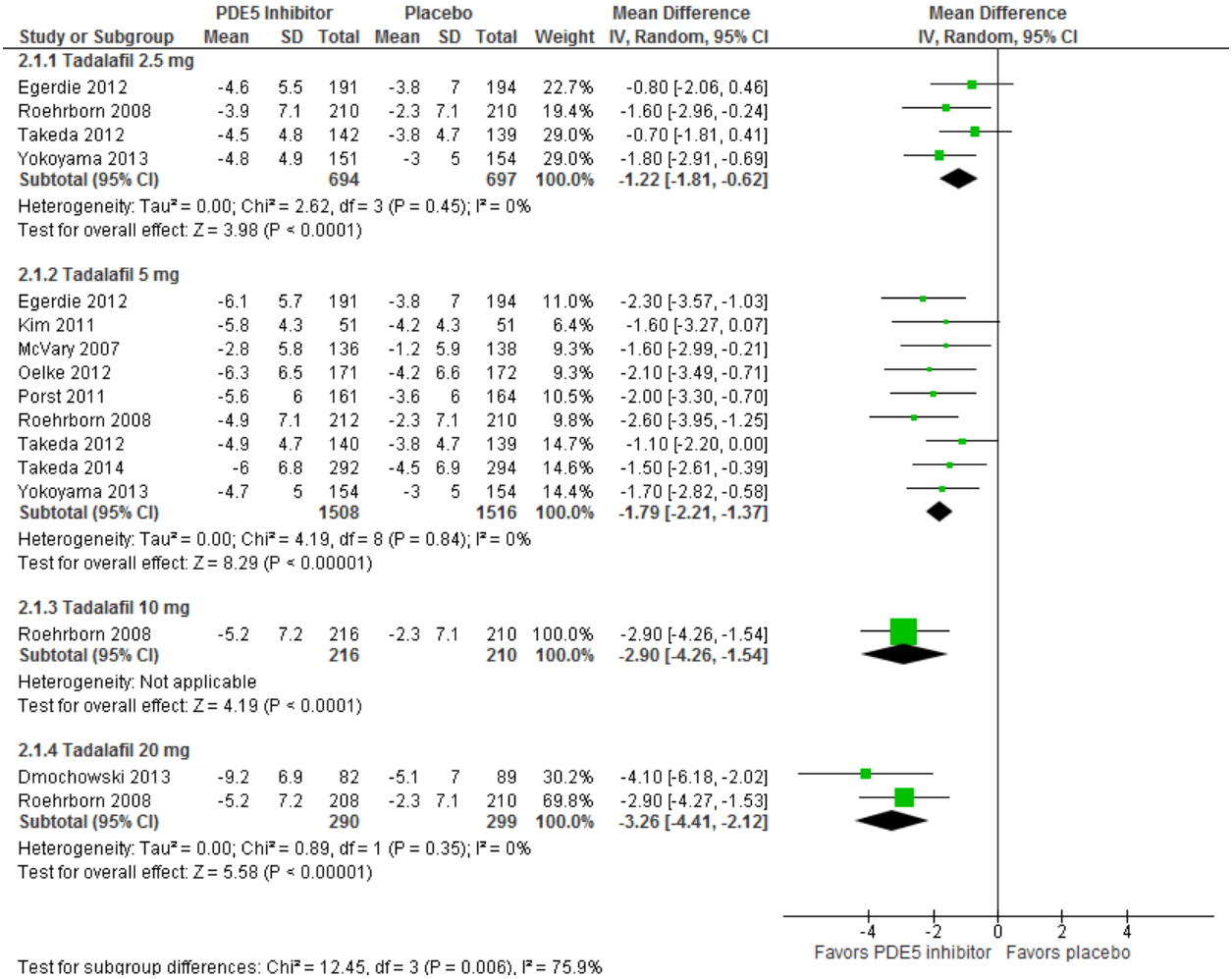


Figure G3. BII, mean change from baseline: tadalafil vs. placebo

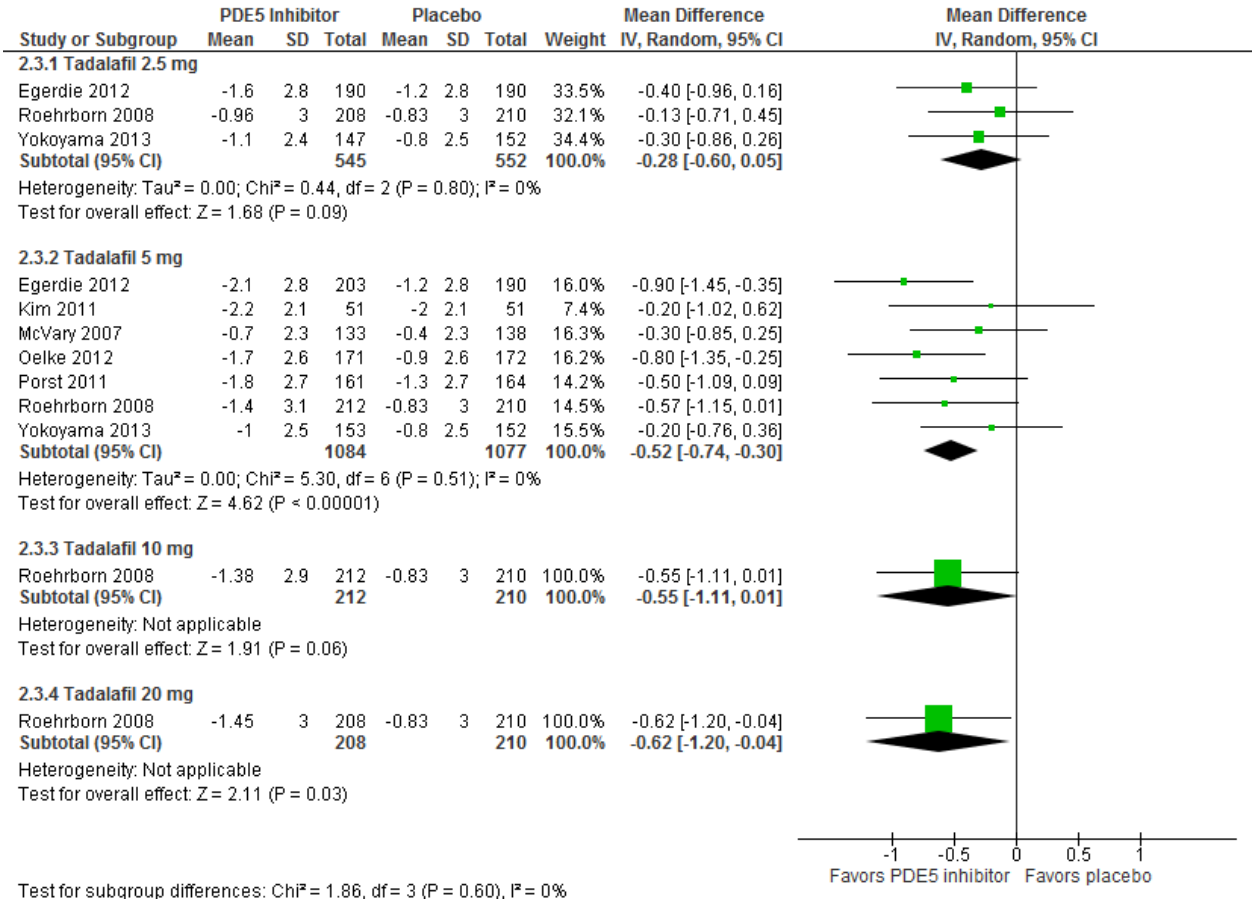


Figure G4. IPSS QoL, mean change from baseline: tadalafil vs. placebo

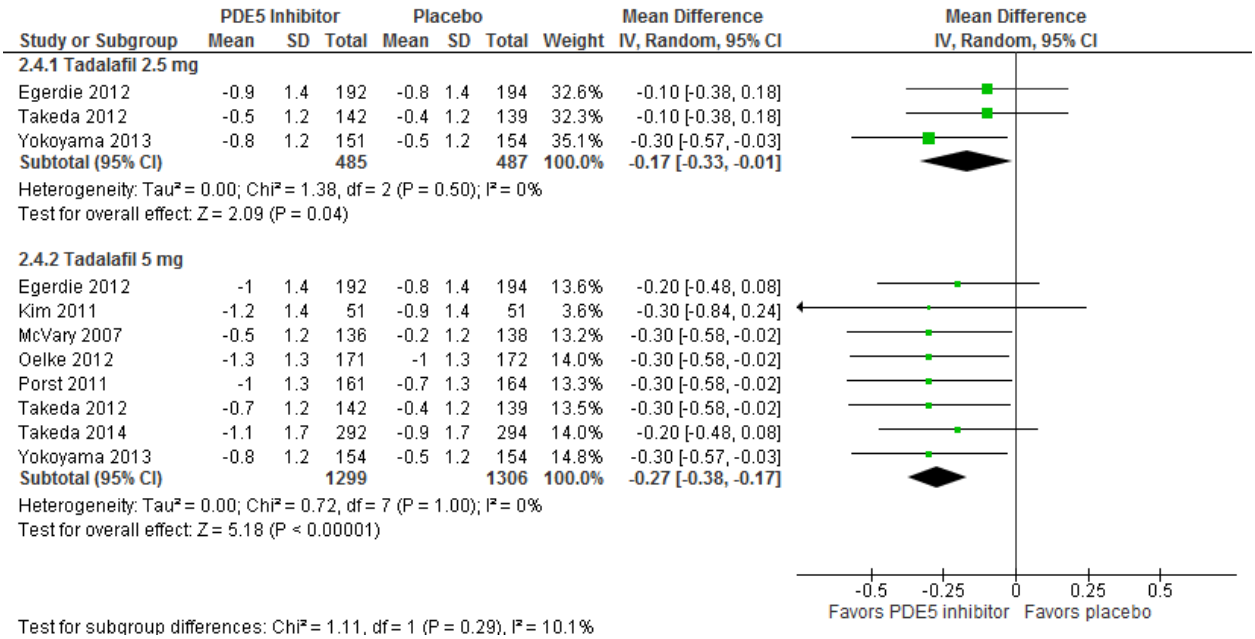


Figure G5. Overall withdrawals: tadalafil vs. placebo

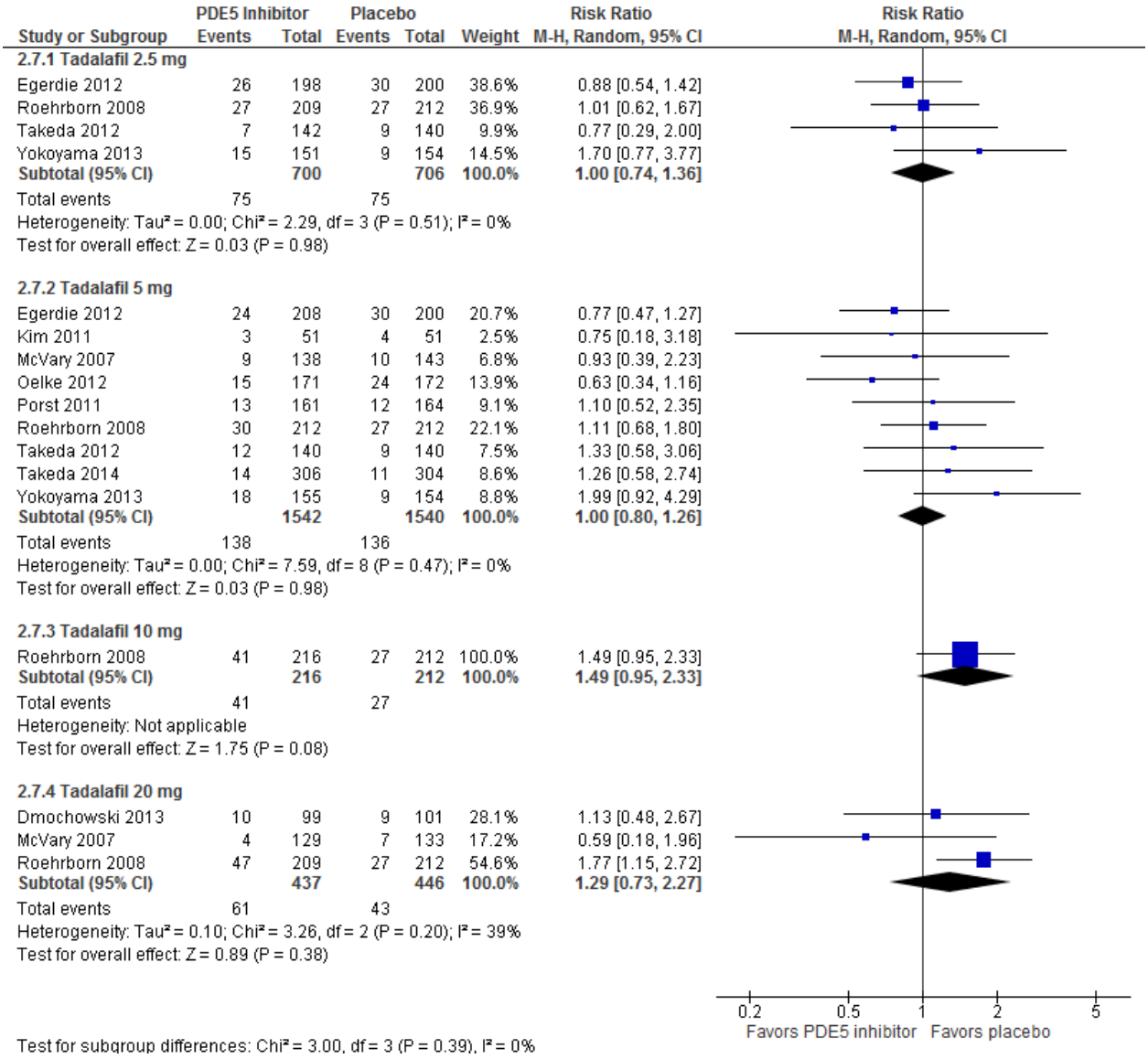


Figure G6. Withdrawals due to adverse effects: tadalafil vs. placebo

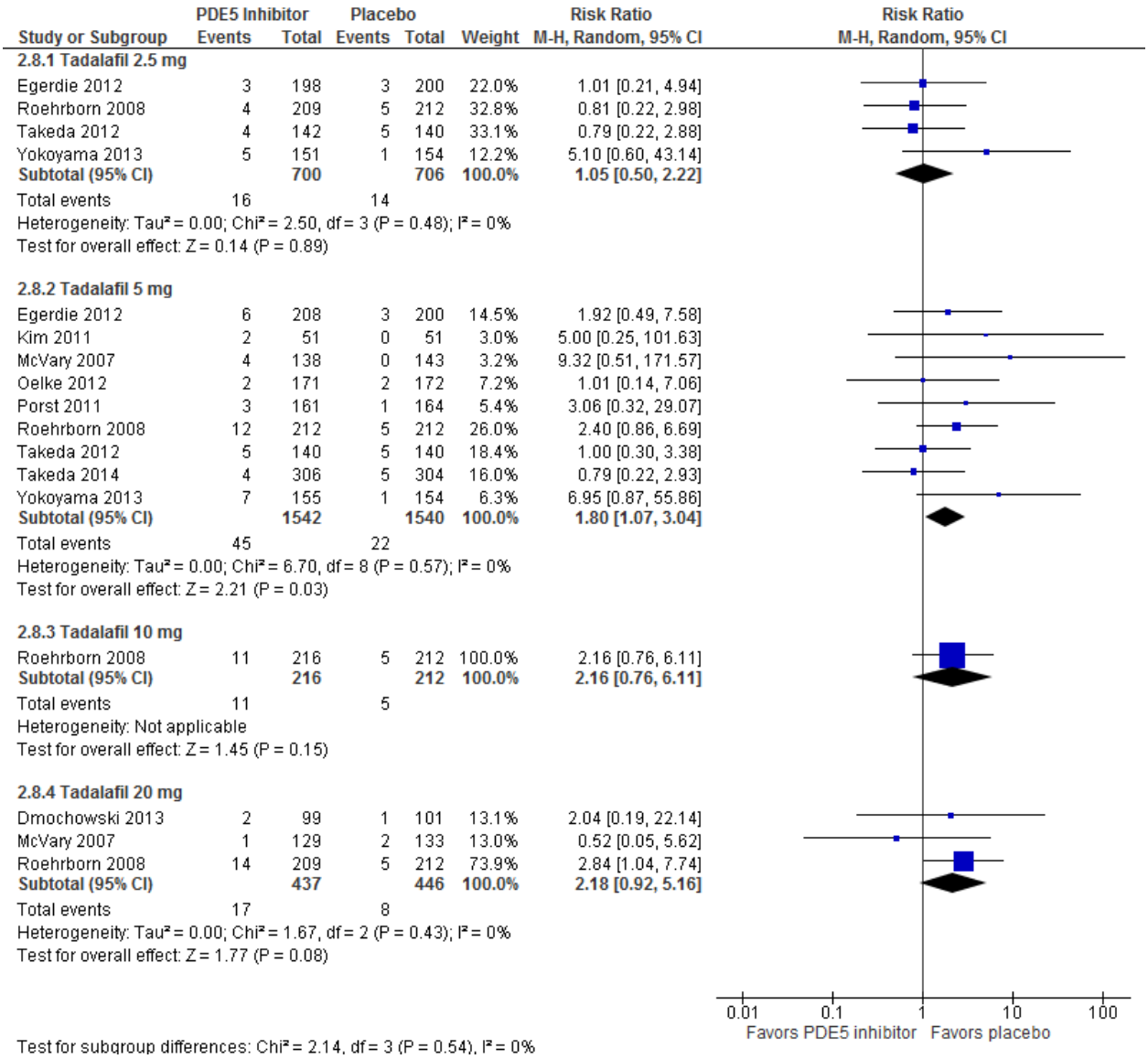
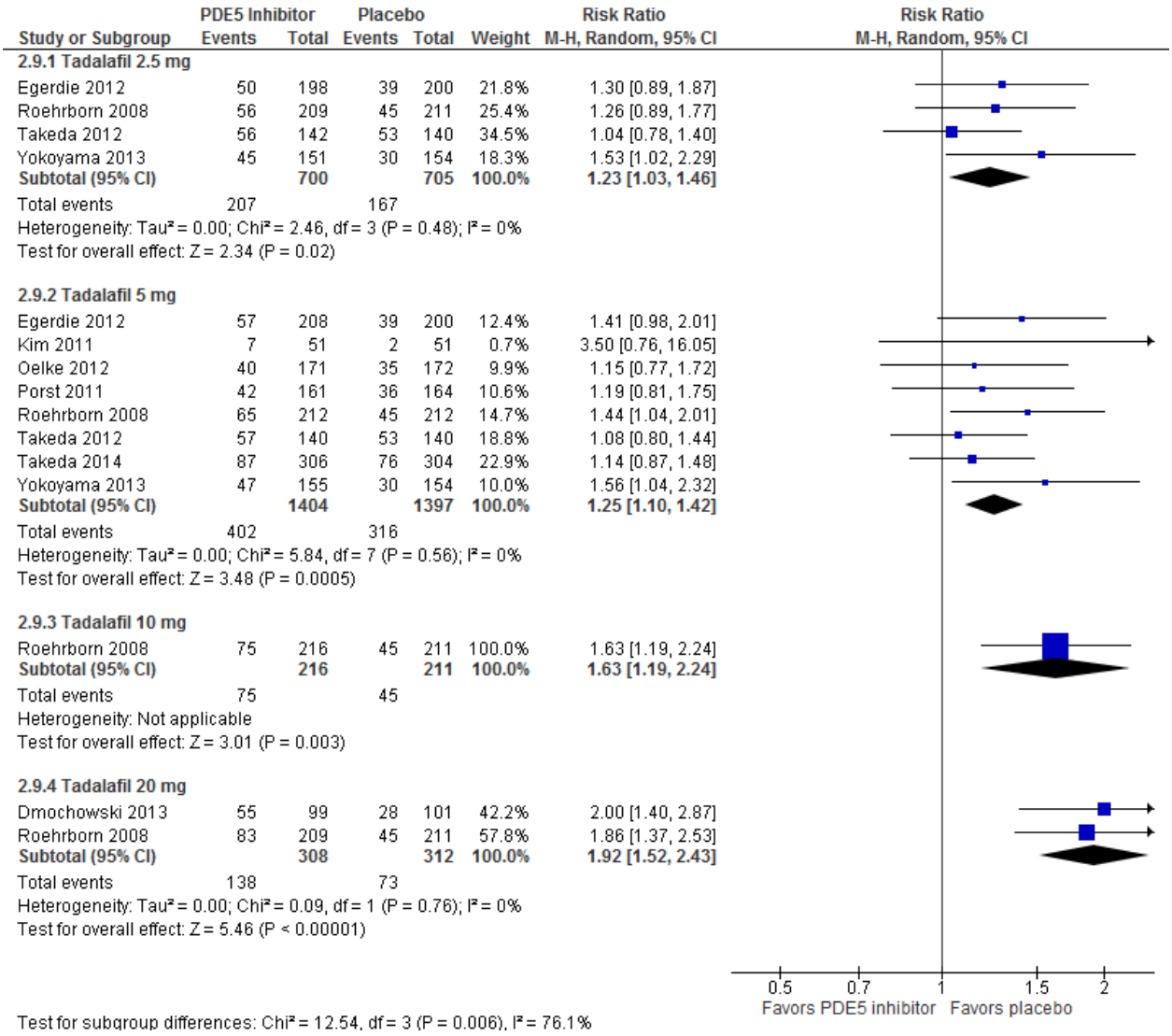


Figure G7. Participants with ≥1 adverse effect: tadalafil vs. placebo



Adjunctive Efficacy of Tadalafil

Figure G8. IPSS scores, mean change from baseline: combined tadalafil + alpha-blocker vs. alpha-blocker

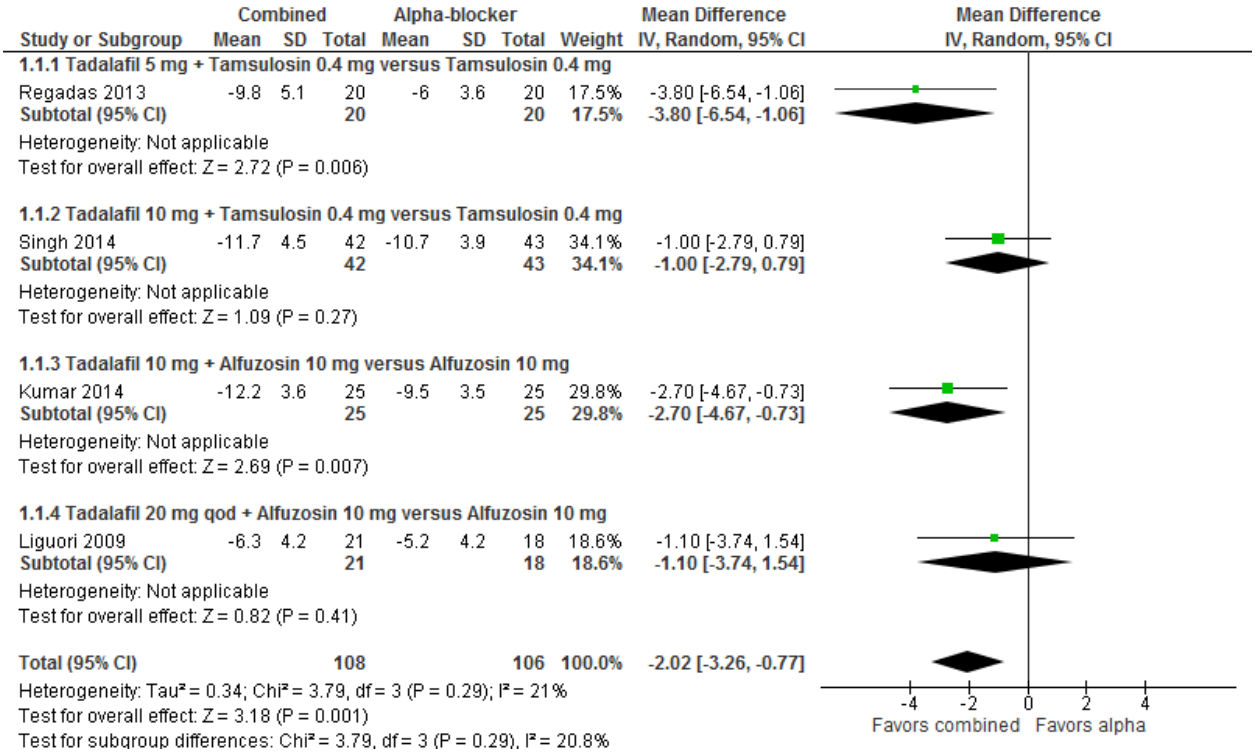


Figure G9. IPSS QoL, mean change from baseline: combined tadalafil + alpha-blocker vs. alpha-blocker

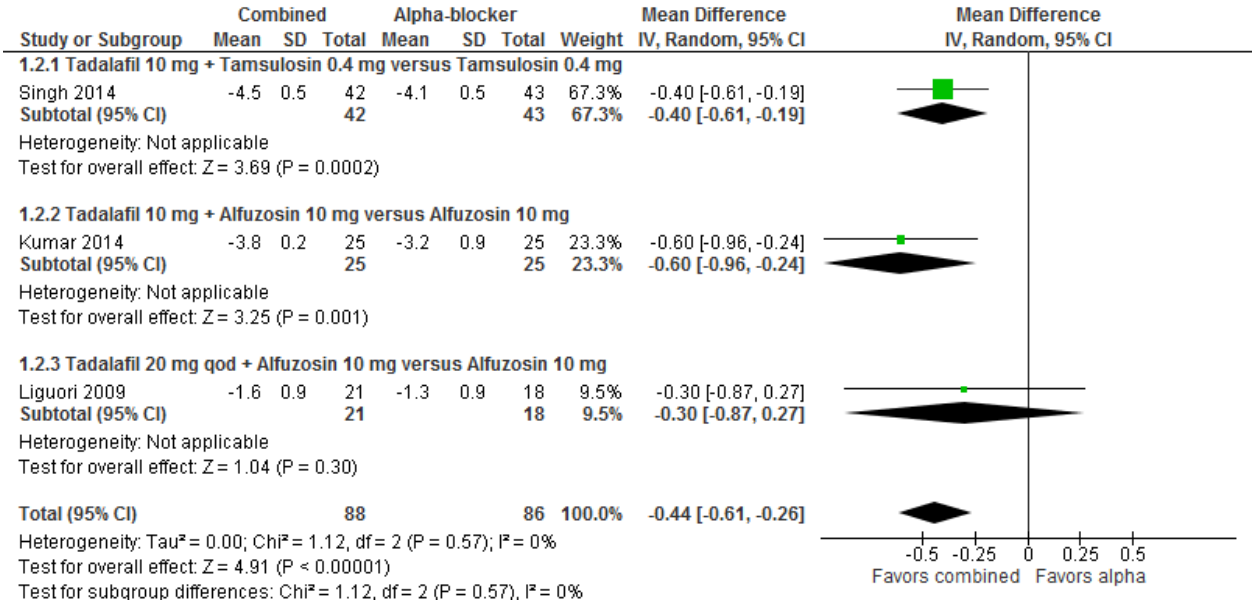


Figure G10. Overall withdrawals: combined tadalafil + alpha-blocker vs. alpha-blocker

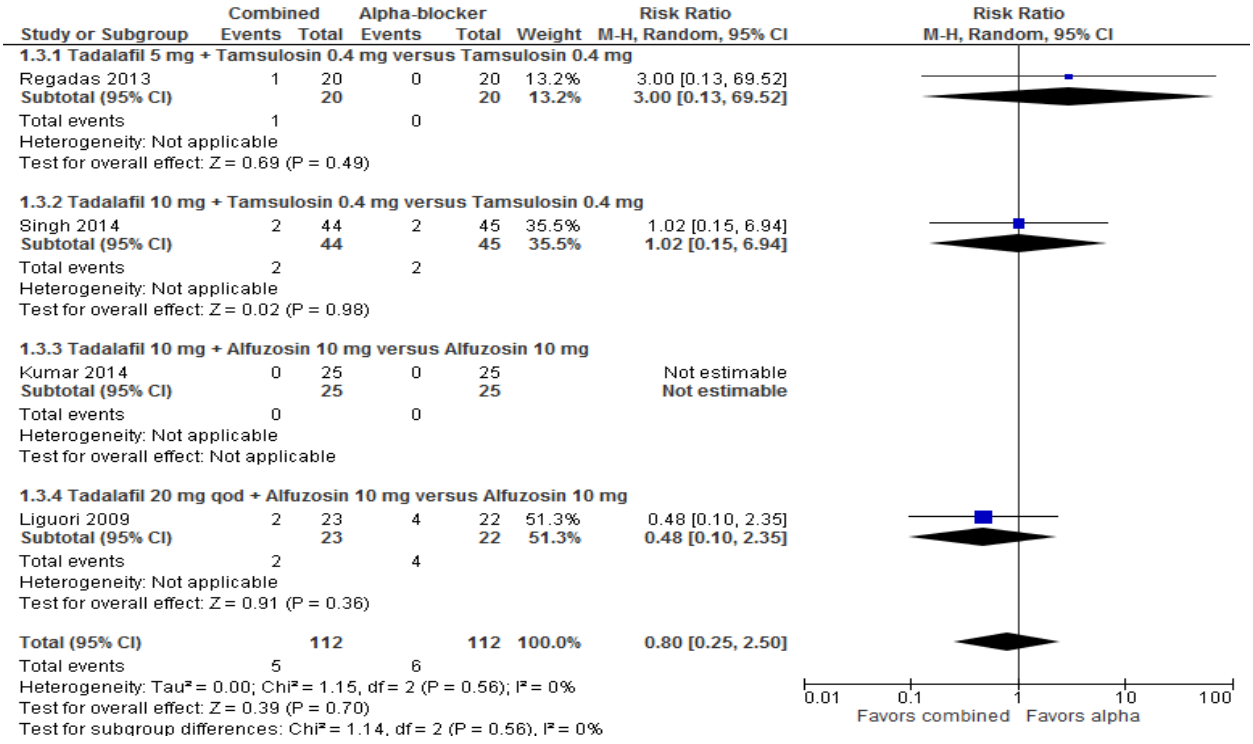


Figure G11. Withdrawals due to adverse effects: combined tadalafil + alpha-blocker vs. alpha-blocker

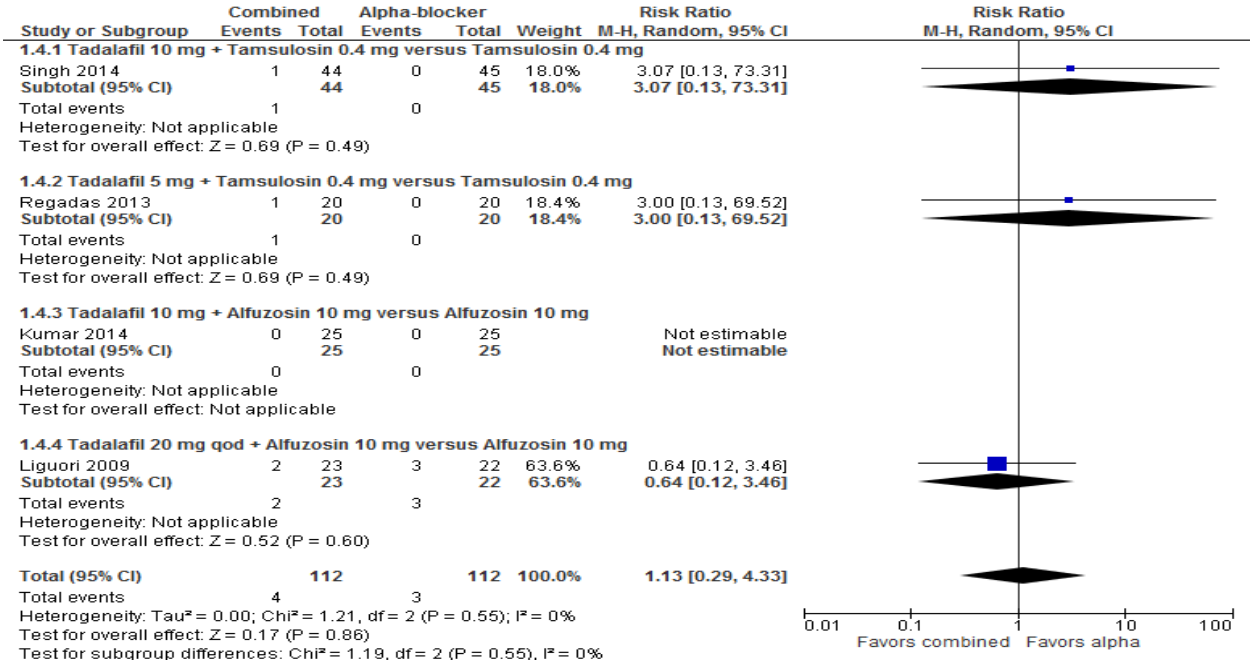


Figure G12. IPSS scores, mean change from baseline: tadalafil vs. tamsulosin

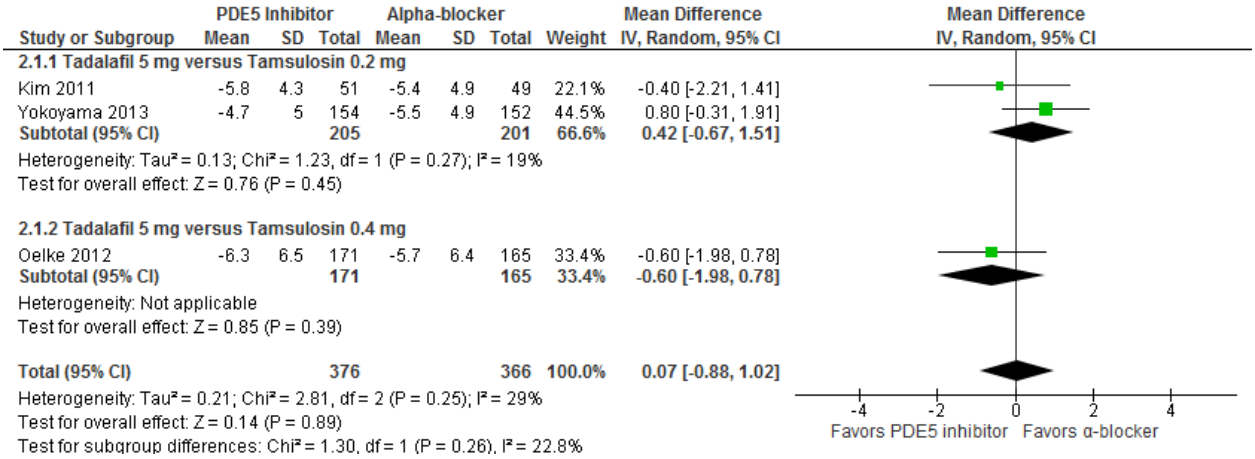


Figure G13. BII scores, mean change from baseline: tadalafil vs. tamsulosin

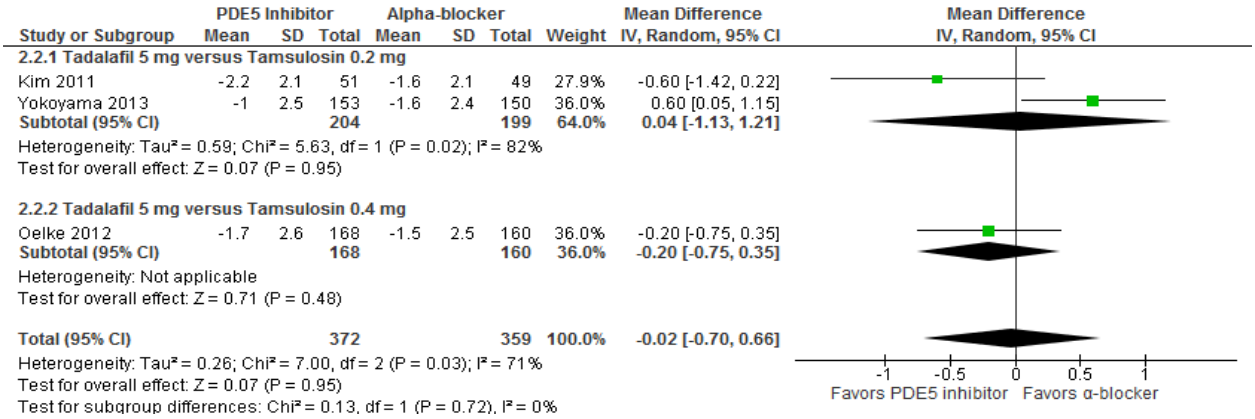


Figure G14. IPSS QoL scores, mean change from baseline: tadalafil vs. tamsulosin

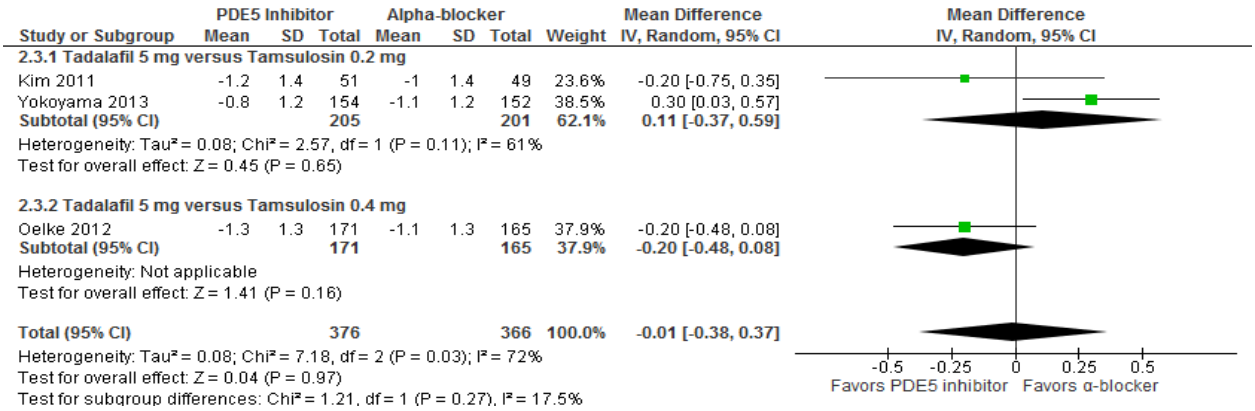


Figure G15. Overall withdrawals: tadalafil vs. tamsulosin

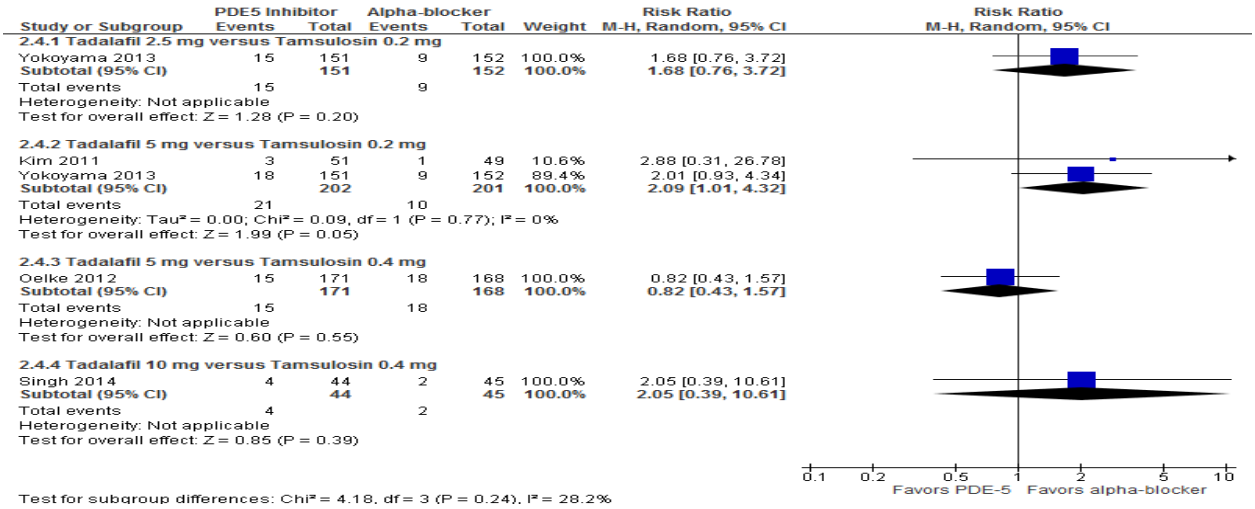


Figure G16. Withdrawals due to adverse effects: tadalafil vs. tamsulosin

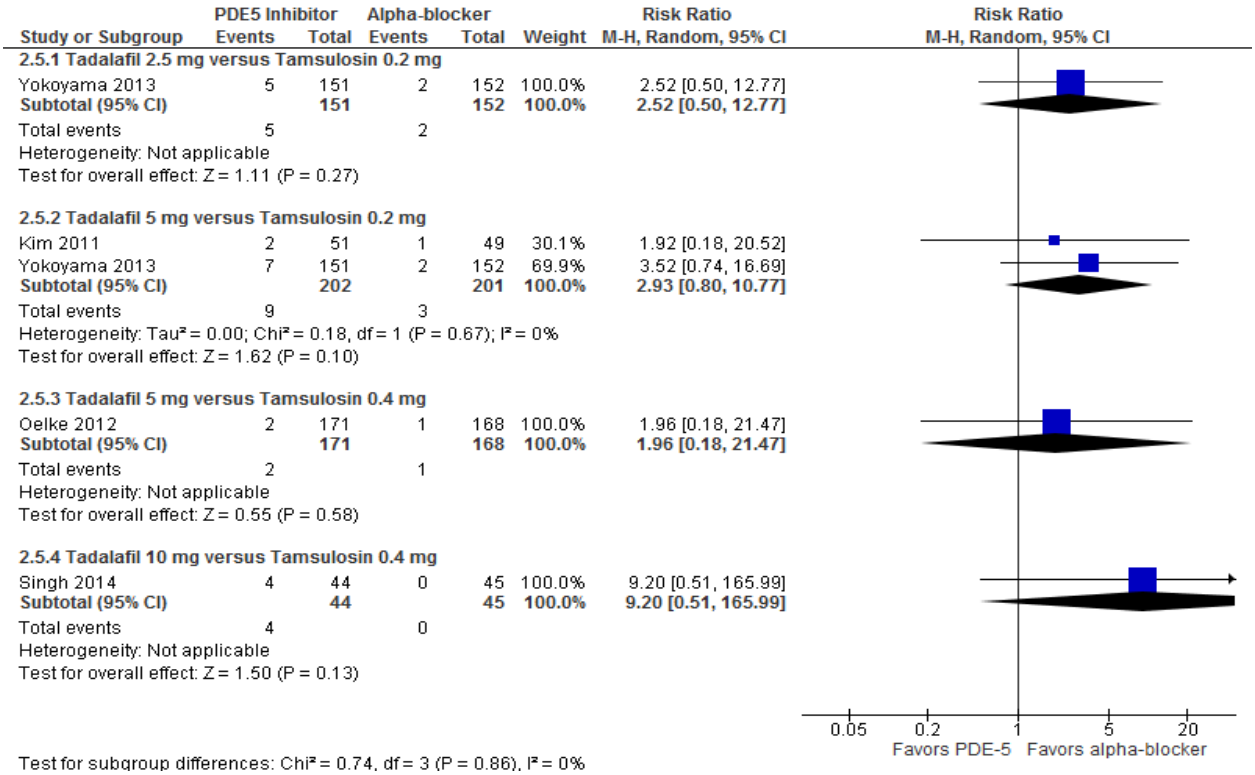
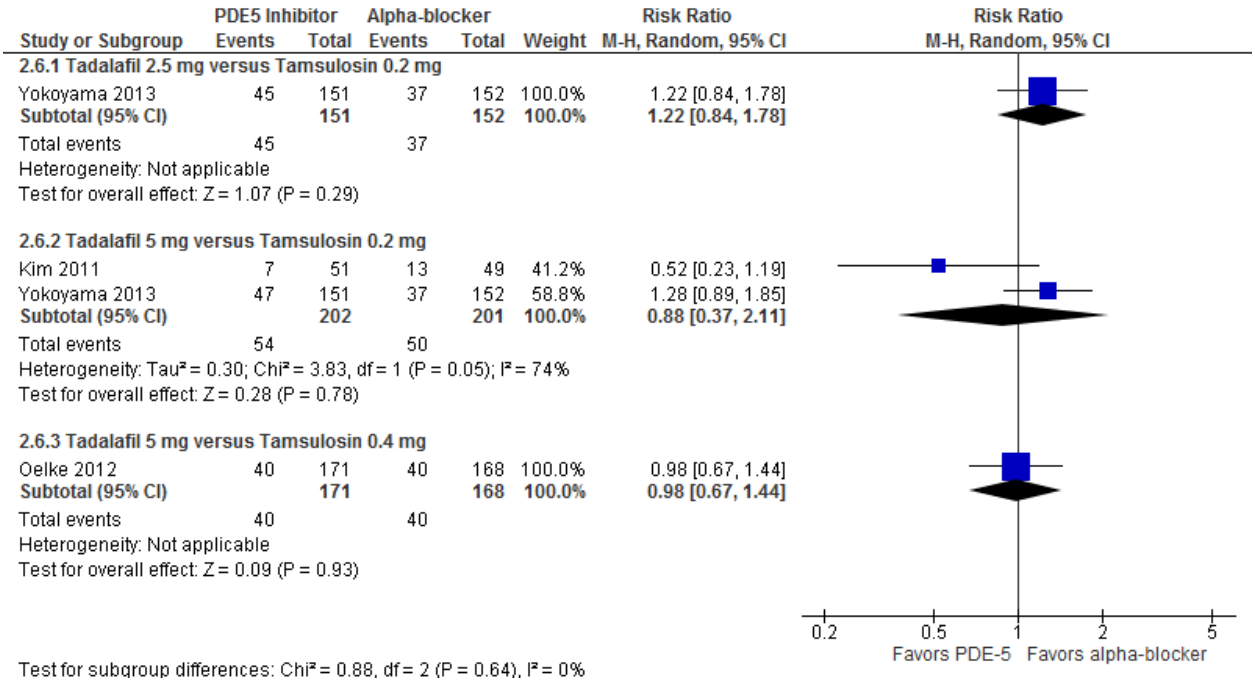


Figure G17. Participants with ≥1 adverse effect: tadalafil vs. tamsulosin



Comparative Effectiveness of Tadalafil Versus Alfuzosin

Figure G18. IPSS scores, mean change from baseline: tadalafil vs. alfuzosin

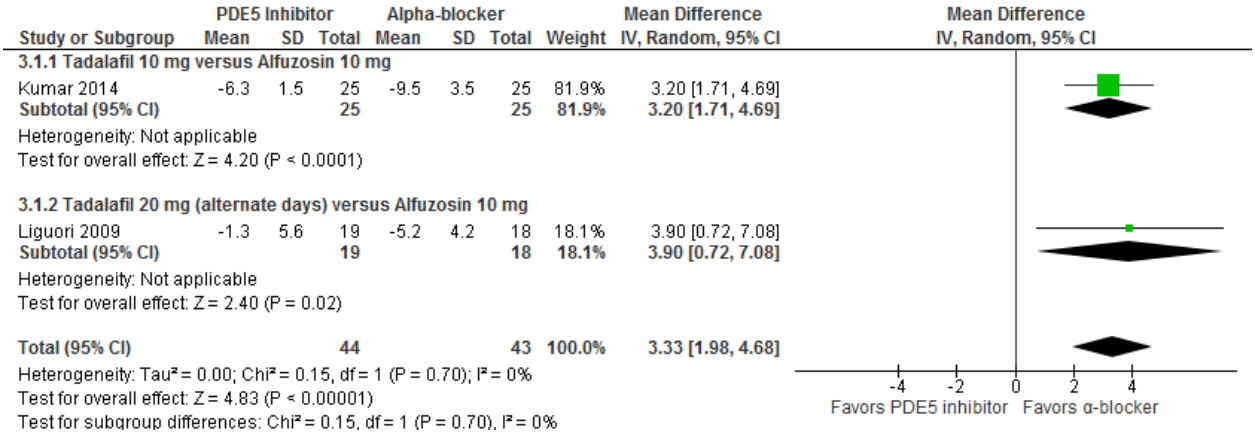


Figure G19. IPSS QoL scores, mean change from baseline: tadalafil vs. alfuzosin

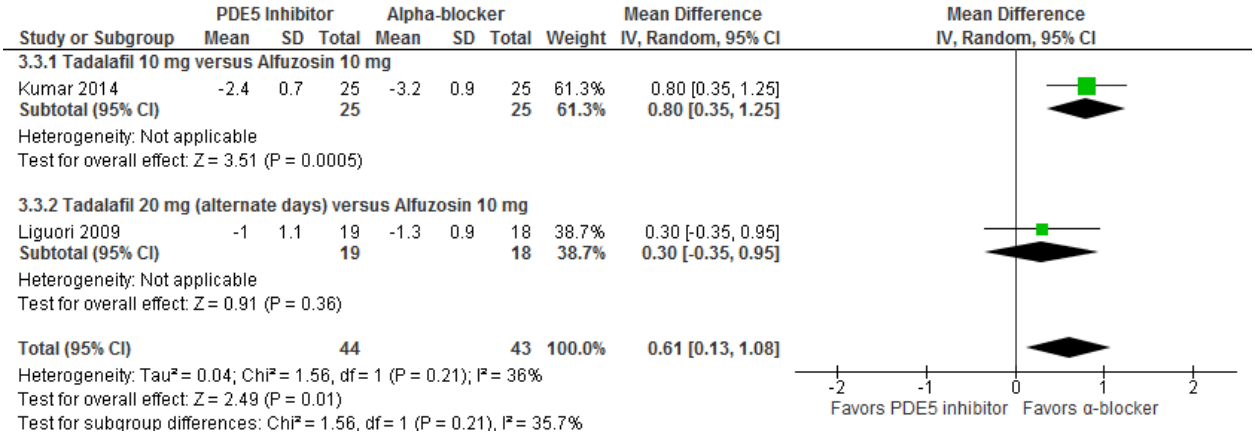


Figure G20. Overall withdrawals: tadalafil vs. alfuzosin

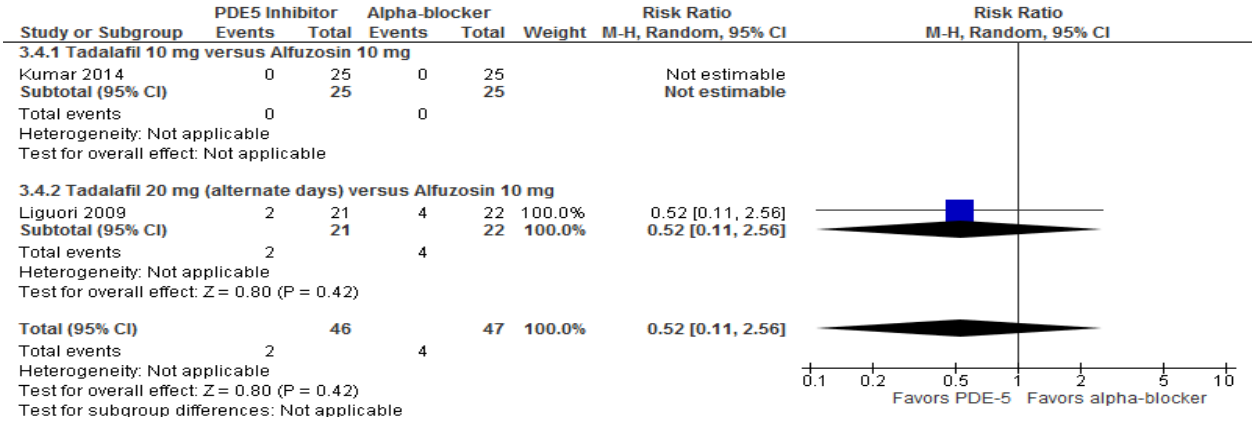


Figure G21. Withdrawals due to adverse effects: tadalafil vs. alfuzosin

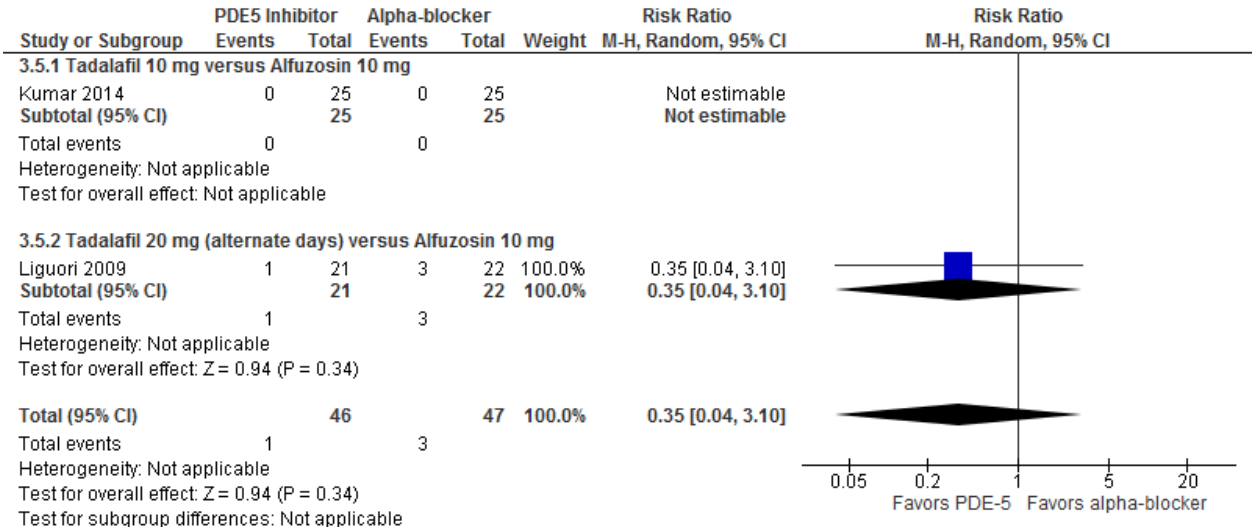


Table G4. Strength of evidence assessments: sildenafil

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Sildenafil 50-100 mg vs. placebo	IPSS/AUA-SI , *mean change from baseline*	1 (341)	MD -4.40 (-6.87 to -1.93)	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	BII, *mean change from baseline*	1 (351)	MD -1.1 [CI NR, P <.0001)]	Low	Direct	Precision unclear	Unknown	Undetected[a]	Insufficient
	IPSS QoL, *mean change from baseline*	1 (351)	MD -0.7 [CI NR, P <.0001)]	Low	Direct	Precision unclear	Unknown	Undetected[a]	Insufficient
	Overall withdrawals	1 (369)	RR 0.80 (0.46 to 1.38)	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Withdrawals due to adverse effects	1 (369)	RR 1.59 (0.59 to 4.28)	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Participants with ≥1 adverse effect	1 (369)	RR 1.22 (0.99 to 1.51)	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
Combined sildenafil 25-50 mg with any alpha-blocker vs. any alpha-blocker	IPSS/AUA-SI , *mean change from baseline*	4 (273)	WMD -1.73 (-3.11 to -0.35) 3 trials MD -1 [CI NR] 1 trial	High	Direct	Imprecise	Consistent	Undetected[a]	Insufficient
	IPSS QoL, *mean change from baseline*	2 (132)	WMD -0.65 (-1.73 to 0.42)	High	Direct	Imprecise	Inconsistent	Undetected[a]	Insufficient
	Overall withdrawals	2 (141)	RR 1.57 (0.54 to 4.55)	High	Direct	Imprecise	Consistent	Undetected[a]	Insufficient
	Withdrawals due to adverse effects	2 (141)	RR 1.43 (0.27 to 7.67)	High	Direct	Imprecise	Consistent	Undetected[a]	Insufficient
Sildenafil 25-50 mg vs. any alpha-blocker	IPSS/AUA-SI , *mean change from baseline*	4 (273)	WMD 0.96 (-0.49 to 2.40) 3 trials MD -1 [CI NR] 1 trial	High	Direct	Imprecise	Consistent	Undetected[a]	Insufficient
	IPSS QoL, *mean change from baseline*	1 (40)	MD -0.80 (-1.18 to -0.42)	High	Direct	Precise	Unknown	Undetected[a]	Insufficient
	Overall withdrawals	1 (45)	RR 0.95 (0.15 to 6.13)	High	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Withdrawals due to adverse effects	1 (45)	RR 0.95 (0.15 to 6.13)	High	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Participants with ≥1 adverse effect	NR							Insufficient

[a] We searched and screened results from clinicaltrials.gov. We identified one eligible trial. This trial has been included, so we detected no publication bias.ARD=absolute risk difference; ARR=absolute risk reduction; BII = BPH Impact Index; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

Efficacy of Sildenafil

Figure G22. IPSS scores, mean change from baseline: sildenafil vs. placebo

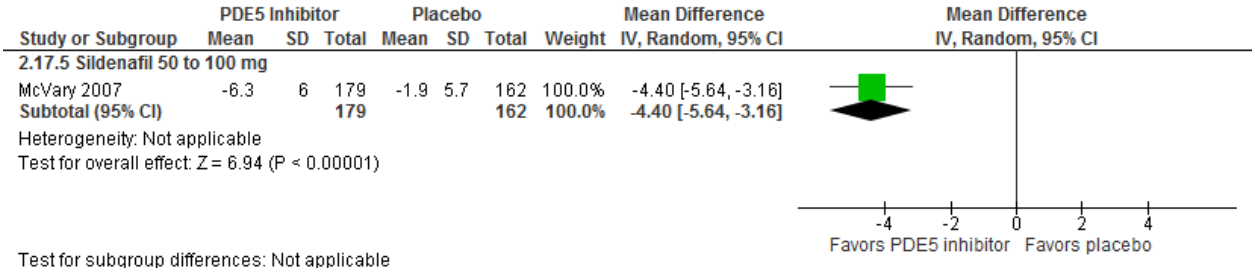
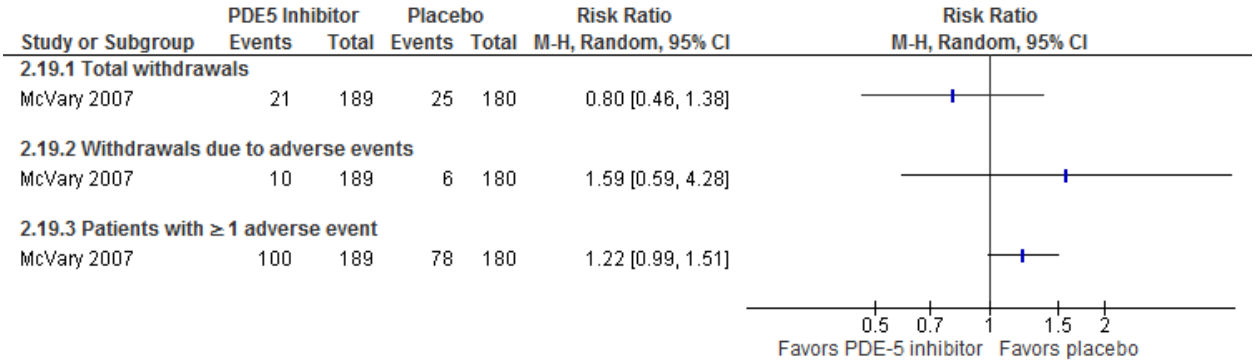


Figure G23. Overall withdrawals, withdrawals due to adverse effects, and participants with ≥1 adverse effect: sildenafil vs. placebo



Adjunctive Efficacy of Sildenafil

Figure G24. IPSS scores, mean change from baseline: combined sildenafil + alpha-blocker vs. alpha-blocker

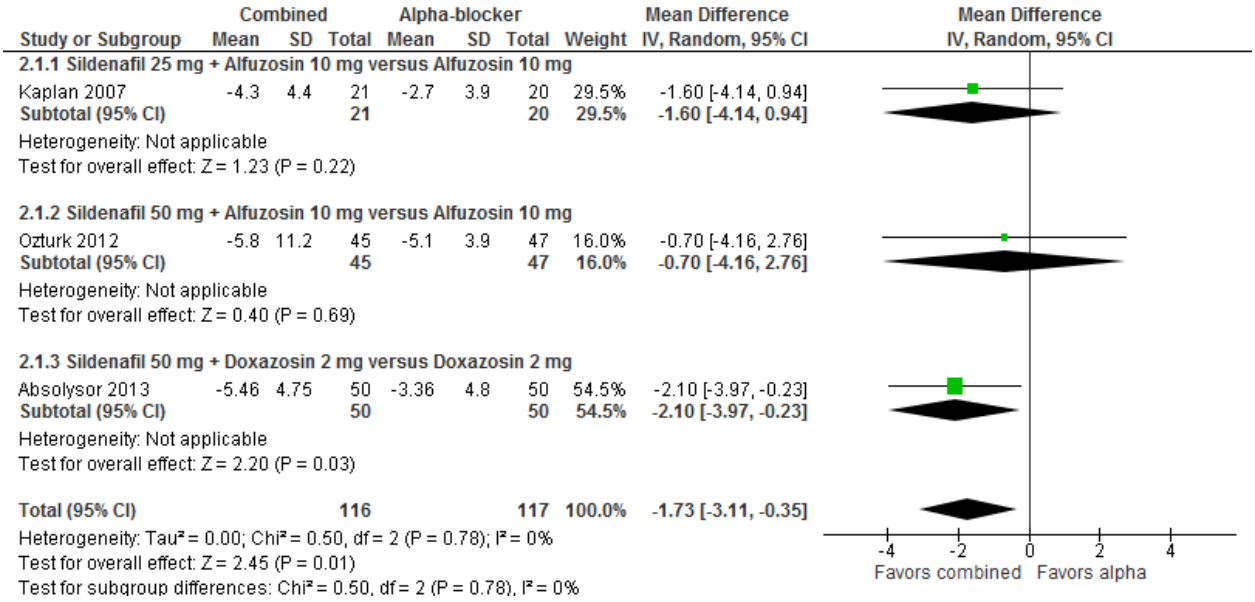


Figure G25. IPSS QoL, mean change from baseline: combined sildenafil + alpha-blocker vs. alpha-blocker

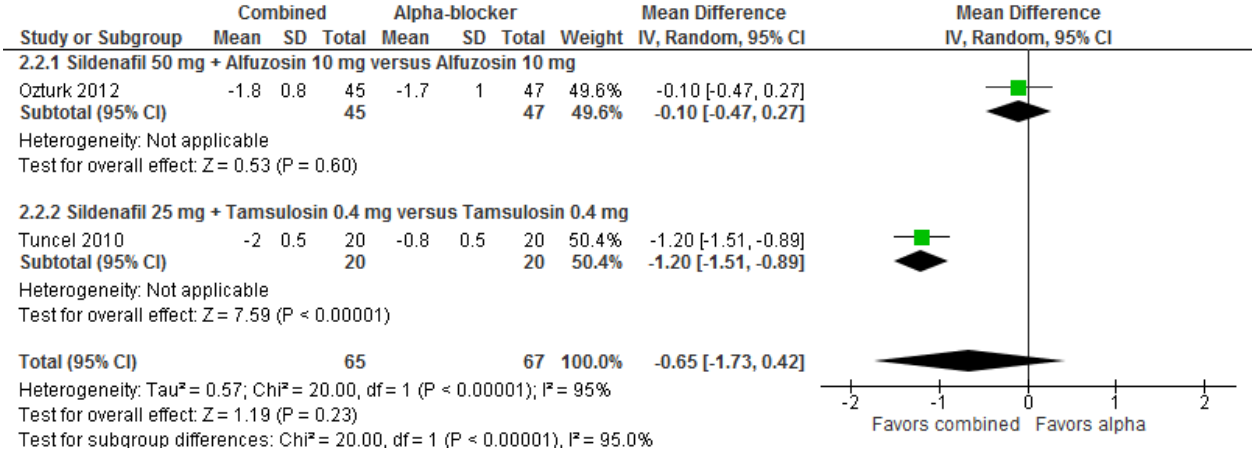


Figure G26. Overall withdrawals: combined sildenafil + alpha-blocker vs. alpha-blocker

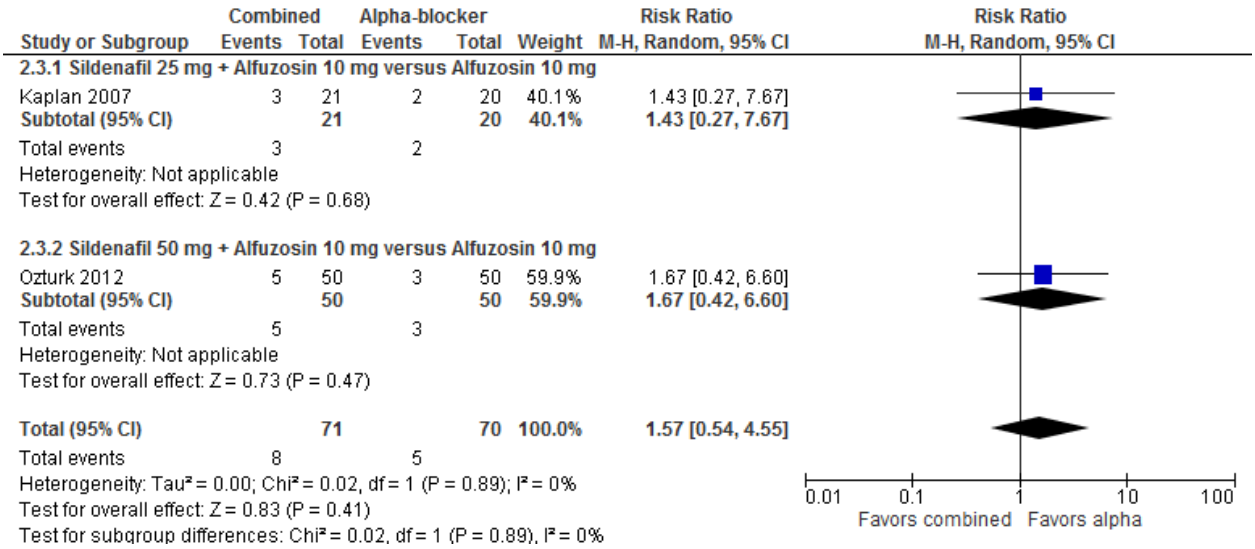
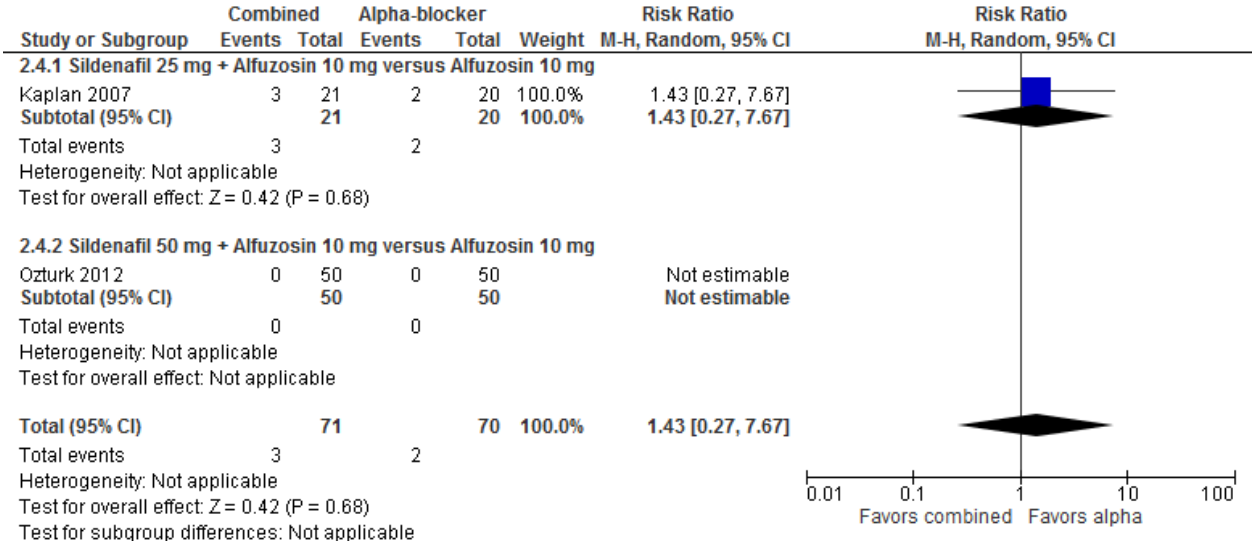


Figure G27. Withdrawals due to adverse effects: combined sildenafil + alpha-blocker vs. alpha-blocker



Comparative Effectiveness of Sildenafil Versus Alpha-Blocker

Figure G28. IPSS scores, mean change from baseline: sildenafil vs. alpha-blocker

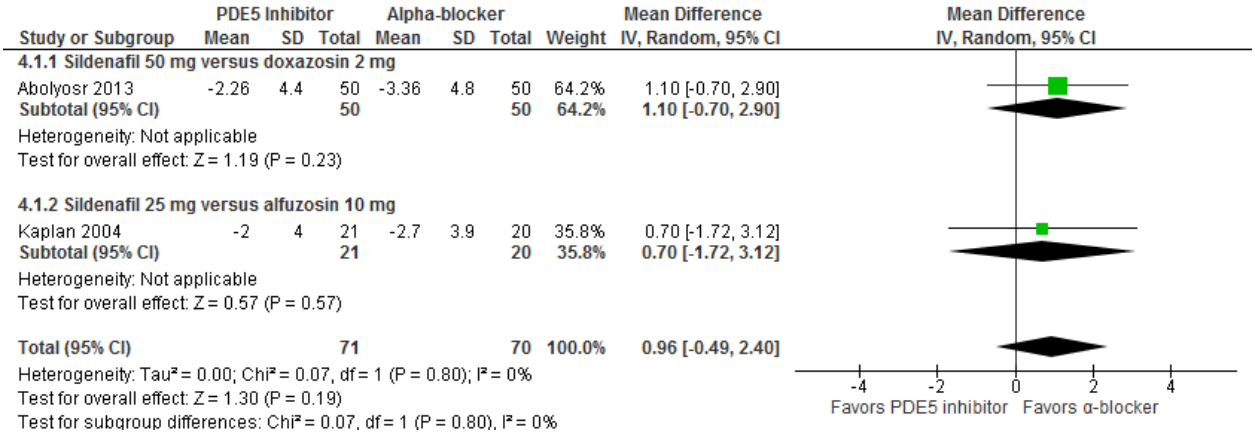


Figure G29. IPSS QoL scores, mean change from baseline: sildenafil vs. alpha-blocker

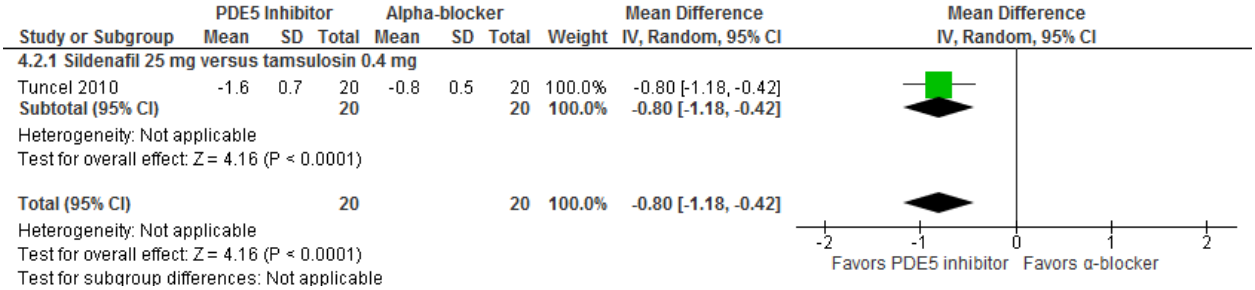


Figure G30. Overall withdrawals and withdrawals due to adverse effects: sildenafil vs. alpha-blocker

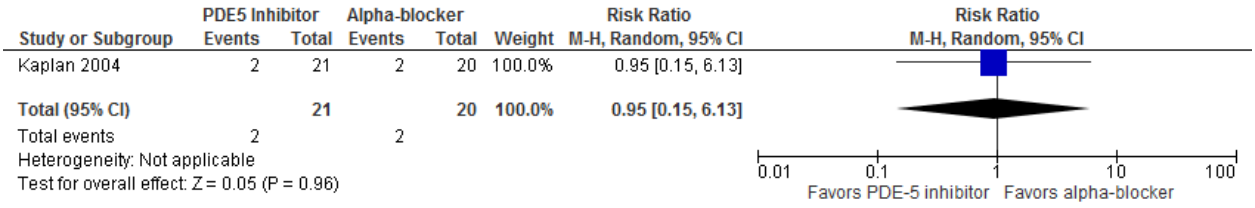


Table G5. Strength of evidence assessments: vardenafil

Comparison	Outcome	# Trials (n)	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Reporting Bias	Evidence Rating
Vardenafil 20 mg vs. placebo	IPSS/AUA-SI , *mean change from baseline*	1 (214)	MD -2.3 (-3.64 to 0-.90)	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Overall withdrawals	1 (222)	0.96 (0.47 to 1.95)	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Withdrawals due to adverse effects	1 (222)	4.67 (1.03 to 21.11)	Low	Direct	Precise	Unknown	Undetected[a]	Low
	Participants with ≥1 adverse effect	1 (222)	1.86 (1.11 to 3.11)	Low	Direct	Precise	Unknown	Undetected[a]	Low
Combined vardenafil 10 mg with any alpha-blocker vs. any alpha-blocker	IPSS/AUA-SI , *mean change from baseline*	1 (60)	MD -2.10 (-4.76 to 0.56)	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Overall withdrawals	1 (60)	RR 0.32 (0.01 to 7.61)	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Withdrawals due to adverse effects	1 (60)	RR 0.32 (0.01 to 7.61)	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient
	Participants with ≥1 adverse effect	1 (60)	RR 1.50 (0.27 to 8.34)	Low	Direct	Imprecise	Unknown	Undetected[a]	Insufficient

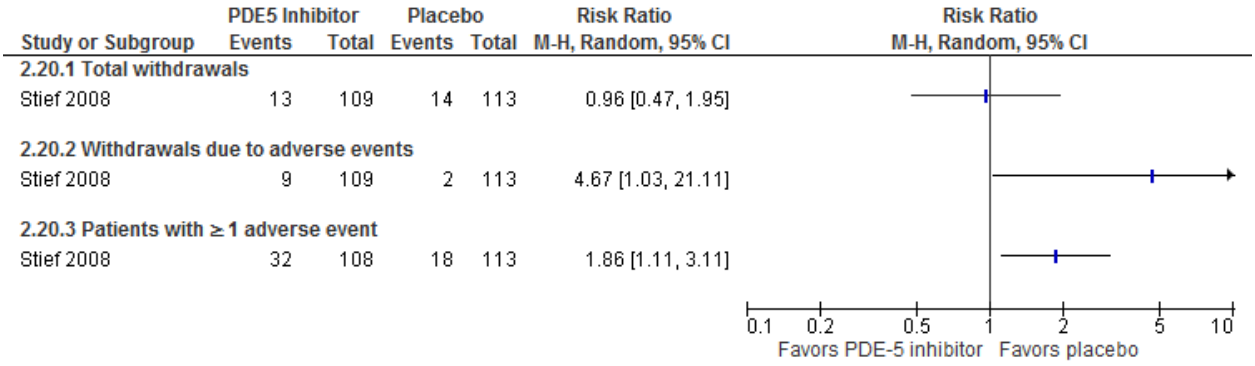
[a] We searched and screened results from clinicaltrials.gov. We identified one eligible trial that has been included. We detected no publication bias.

ARD=absolute risk difference; ARR=absolute risk reduction; BII = BPH Impact Index; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (*Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

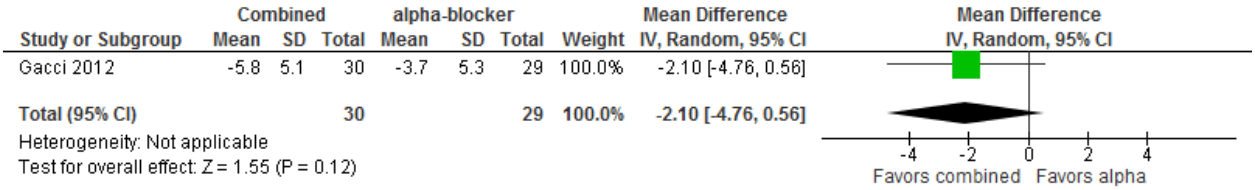
Efficacy of Vardenafil

Figure G31. Overall withdrawals, withdrawals due to adverse effects, and participants with ≥1 adverse effect: vardenafil vs. placebo



Adjunctive Efficacy of Vardenafil

Figure G32. IPSS scores, mean change from baseline: combined vardenafil + alpha-blocker vs. alpha-blocker



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